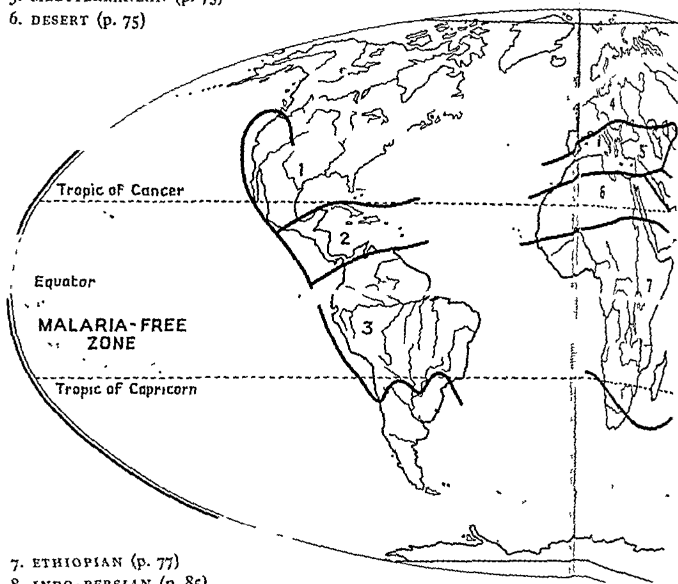
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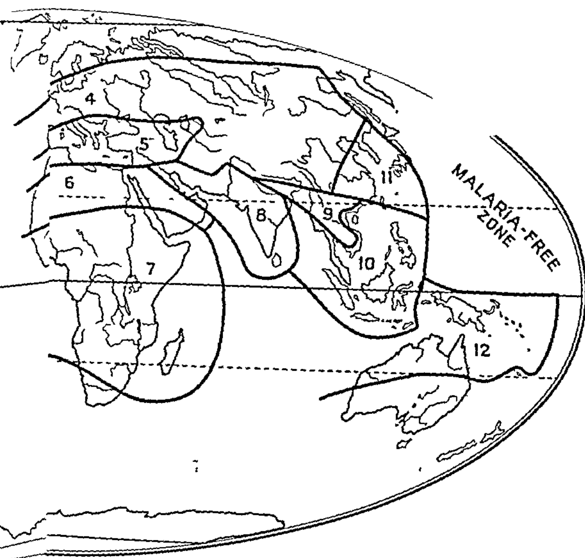
ZONES

1. NORTH AMERICAN (p. 67)
2. CENTRAL AMERICAN (p. 68)
3. SOUTH AMERICAN (p. 69)
4. NORTH EUROPEAN AND ASIATIC (p. 71)
5. MEDITERRANEAN (p. 73)
6. DESERT (p. 75)



7. ETHIOPIAN (p. 77)
8. INDO-PERSIAN (p. 85)
9. INDO-CHINESE HILLS (p. 89)
10. MALAYSIAN (p. 90)
11. CHINESE (p. 93)
12. AUSTRALASIAN (p. 95)

THE ZONES OF MALARIAL EPIDEMIOLOGY



Front Endpaper

THE EPIDEMIOLOGY AND CONTROL OF MALARIA



G. MACDONALD, 1903-1967

THE EPIDEMIOLOGY AND CONTROL OF MALARIA

BY

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CONTENTS

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CONTENTS

LIST OF ILLUSTRATIONS

FIGURES

TABLES

LIST OF ILLUSTRATIONS

FIGURES

TABLES

the fault could not lie in mathematical technique The premises on which that analysis was made were therefore examined, and were identical through all the works One seemed unsound the premise stated or implied in mathematical working that an individual infected with malaria could not be again infected until after complete recovery from the initial infection This is certainly untrue, it has been shown to be so in experiment and natural happenings cannot be explained except by its denial The converse premise that superinfection does occur can be established, though it is admitted that this does not lead to assurance of its universal possibility A mathematical model was attempted with this as one of the premises and supplied models of happenings which were related to nature From this has developed a series of studies in which I have freely referred to Dr J O Irwin and Dr P Armitage of the Medical Research Council Statistical Unit in this School, receiving liberal help for which I am grateful Together these studies build up into a complete picture of the epidemiology of malaria Exactness it can never claim, but realistic representation of natural happenings is there

Together with this desk study there has been considerable laboratory and field work, much of which has been undertaken by my colleagues Dr C C Draper and Mr G Davidson, without whose collaboration the viewpoint could not be taken as established Mr Davidson has continued researches on resistance to insecticides, and the statement on that subject derives from his work carried out in the Ross Institute insectaries

The theory of control was originally built up on a general basis but has needed elaboration with reference to the recent programmes of malaria eradication which has also led to further analysis of epidemic happenings The World Health Organization has played a leading part in these programmes, and I am grateful to the Chief of the Malaria Section, Dr E J Pampana, for his appreciation of the utility of this type of study and for his stimulation to pursue it when interest flagged

The fundamental mathematical papers in which the subject was explored were published in the *Tropical Diseases Bulletin*, and I am very grateful for the audacity of the Editor, Dr C Wilcocks,

in publishing such an odd venture Other papers have been published in the *Bulletin of the World Health Organization*, the *Indian Journal of Malariology* and the *Proceedings of the Royal Society of Medicine* This material has been drawn on in making the present wider statement of the subject and Dr Wilcocks has permitted reproduction of one section and several illustrations, for which I thank him My grateful thanks are also due to the Director General of the World Health Organization, to the Chief of the Technical Publications Section and Dr E J Pampana, Chief of the Malaria Section, for permission to reproduce Figures 8 and 9 from the *Bulletin of the World Health Organization*, details of the Busvine and Nash technique from the Fifth Report of the Expert Committee on Malaria, and the details of chemical tests of insecticides in Appendix II which are extracted from *Specifications for pesticides, insecticides, rodenticides, molluscicides, and spraying and dusting apparatus* I am also much indebted to Miss E M Bulter for her interest, capability and industry in preparation of the script

The deliberate intention of the short list of references at the end of each chapter is not to be all inclusive but primarily to refer the reader to sources from which he may extend his studies In selecting references preference has been given to those which review knowledge and which include a considerable bibliography Our knowledge of epidemiology is founded on a great accumulation of facts and there is no collection of material and source of factual information comparable with that in Boyd's *Malariology* to which the reader may always usefully refer, and several chapters of which are quoted A smaller but still extensive source is in *Practical Malariology* by Russell, West and Manwell This primary objective of the references is supplemented by a secondary objective of referring to key papers on the subject discussed in the relevant chapter and often published after the main reviews mentioned, and hence a number of individual papers or reports are quoted Since the development of the approach has been for some years the main concern of my close colleague Mr G Davidson and for some time that of Dr C C Draper, it is natural that their publications should be frequently mentioned

Altogether I have received much help, but I cannot for that reason disclaim responsibility for the whole, which is a new picture of malaria and its control as seen by an epidemiologist with many valued friends and helpers

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June, 1957

Extract from *The prevention of malaria* by Sir Ronald Ross, 2nd Edition, 1911, p 651

"66 *Theory of Happenings* (1) *Previous Work* —The mathematical treatment adopted in section 28 has been met with some questioning by critics Some have approved of it, but others think that it is scarcely feasible owing to the large number of variables which must be considered As a matter of fact all epidemiology, concerned as it is with the variation of disease from time to time or from place to place, *must* be considered mathematically, however many variables are implicated, if it is to be considered scientifically at all To say that a disease depends upon certain factors is not to say much, until we can also form an estimate as to how largely each factor influences the whole result And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at issue"

CHAPTER I

THE FORMS OF EPIDEMIOLOGY

This book is largely an experiment in putting forward a novel attitude to the epidemiology of malaria, being the presentation in ordinary language of the products of a mathematical study. This has seemed to give some new and fruitful concepts of the epidemiological features of insect-borne disease, and malaria in particular, which deserve interpretation from their original technical form into one suitable for everyday use.

To explain them and show the ways in which a new attitude might be helpful demands some preliminary consideration of the nature of epidemiology itself. The science as a whole deals with the reasons for the prevalence of disease and the nature and causes of variations in it. It is one of the oldest medical studies, having originated in a scientific form in the time of Hippocrates. From that time up to the middle of the nineteenth century it was concerned very largely with the circumstances in which disease occurred, either in a static form or as epidemics, and it might be properly called circumstantial epidemiology. It reached a considerable degree of understanding; indeed a classical malaria survey made over a century ago by Baker, Dempster, and Yule and based solely on circumstantial evidence without knowledge of either parasite or vector could hardly be bettered to day. The authors were able to define the communal characteristics of the disease, to measure its prevalence by means of the spleen rate which they devised, to understand the surroundings which favoured its production, and to prescribe the measures which would be necessary to reduce its incidence in the area which they studied or to prevent outbreaks following irrigation work in other similar ones. There were considerable generalisations from this type of circumstantial knowledge which made it possible to avoid the disease and in some cases to control it. Those who doubt this might well refer to the voluminous writings of Hirsch.

In the second half of the nineteenth century circumstantial study was first supplemented and later largely replaced by

was doubled? Or if the number remained unchanged, but they took to biting man twice as frequently as before? Clearly the amount of malaria would rise, but biological data give us no idea of the proportion which the rise would bear to the increase in the number of mosquitoes or the frequency of feeding on man, and not even an indication whether the rise would be the same following either of these two happenings The explanation of the relationship between one event and another is the sense of proportion which is lacking It can only be supplied by the addition of a third type of epidemiology—the mathematical branch It is the object of the present work to describe the epidemiology and control of malaria with the help of the additional light which mathematical epidemiology can throw on them

The aim of mathematical epidemiology is to integrate biological and circumstantial data into one coherent whole, with the other two branches it completes the science of epidemiology Emphatically it gives a sense of proportion, relating the various factors of the transmission cycle to each other and to relevant biological characteristics of the mosquito It can show the scale of changes in infection rates to be expected following changes in one of the transmission factors, and why this scale should differ greatly under different conditions It can supply the principle which connects happenings in two countries and explain the detail of happenings in any individual country It does not attempt to usurp the place of either of the other branches, being dependent on both, but to round them off as a complete whole, giving a rational understanding of disease

Some mathematical ability is an essential part of the stock-in-trade of the man who would develop or criticise the subject, though little is demanded of him who would only wish to understand its implications and conclusions The only essentials for this are a willingness to tackle a strange subject, an understanding of metric and logarithmic graphs, and an occasional effort to utilise a formula simplified by tables of the value of its main component parts It is hoped that as many as possible will attempt the full understanding and that others will surmount the small obstacles in their way To this end the verbal and algebraic

statements are separated except for the occasional use of an algebraic expression in the text

The development of the epidemiological approach can be studied in —

HIPPOCRATES With an English translation by W. H S Jones *Airs, waters, places*, 1, 71–137, and *Epidemics*, 1, 147–185 London William Heinemann, 1923

BAKER, W E, DEMPSTER, T E & YULE, H Report of a committee assembled to report on the causes of unhealthiness which has existed at Kurnaul 1847, reprinted 1929, *Rec. Malar Surv India*, 1, No 2, 1–68 (The origin of the spleen rate is on pp 69–85)

HIRSCH, A *Handbook of geographical and historical pathology* Translated by Charles Creighton, 1, Chapter VII London New Sydenham Society, 1883

GILL, C A *The genesis of epidemics and the natural history of disease* London Bailliere, Tindall & Cox, 1928

HAMER, Sir WILLIAM *Epidemiology, old and new* London Kegan Paul, Trench, Trubner & Co Ltd, 1928

and there is an excellent review of attitudes towards epidemiology in —

RUSSELL, P F *Man's mastery of malaria* London Oxford University Press, 1955

The history of the mathematical analysis of malaria can be traced in —

ROSS, R *The prevention of malaria*, pp 651–686 2nd edition London John Murray, 1911

ROSS, R An application of the theory of probabilities to the study of *a priori* pathometry, Pt I 1916, *Proc roy Soc*, A, 92, 204–230

WAITE, H Mosquitoes and malaria 1910, *Biometrika*, 7, 421–436

LOTKA, A J Contribution to the analysis of malaria epidemiology V Summary 1923 *Amer J Hyg*, 3, January supplement, 113–121

KERMACK, W O & MCKENDRICK, A G A contribution to the mathematical theory of epidemics 1927, *Proc roy Soc*, A, 115, 700–721

The papers on which the present expositions are based are listed in the bibliography at the end of Appendix I

CHAPTER II

THE CYCLE OF TRANSMISSION

STAGES IN MAN

MALARIA in man is the state of infection with one of the four plasmodia *Plasmodium falciparum*, *P vivax*, *P malariae* or *P ovale*, the life history of each of which is similar in principle though there are considerable differences in detail After inoculation of sporozoites there is a preliminary stage of development in the liver of exo-erythrocytic forms during a "pre-patent" period, which may be prolonged in vivax infections, and which ends with the liberation of merozoites into the blood where they invade the red cells The initial liberation is too small in number to give either clinical effects or an observable parasitaemia by microscopic examination, though it can be demonstrated by sub inoculation of blood into susceptible persons These erythrocytic forms multiply, and at first apparently in an unrestricted manner with the result that in a few days observable parasitaemia and clinical effects are produced Within about a week of first patency there is a marked reduction in the rate of this multiplication, and in this way some balance of numbers is reached, usually with a fairly dense parasitaemia approaching 100,000 parasites per mm^3 of blood The initial period of parasitaemia thus launched continues for a variable but usually lengthy period of time in which an early immunity is demonstrated by a slow and irregular decrease in parasite density It is followed by a period of irregular parasitaemia consisting of periods in which parasites are alternately present in and absent from the blood, but with a general tendency towards a decrease in numbers of parasites, increase in the length of parasite-free periods, and shortening of the periods of patency

In the case of *P falciparum* there is no fresh source of erythrocytic forms after the termination of the first pre erythrocytic cycle, the entire period of infection is in reality one of continuous parasitaemia, though the varying numbers of parasites in the peripheral blood give a picture of alternate infection and freedom

from it It is certain in the case of *P vivax*, and probable in the case of the other two parasites, that secondary exo erythrocytic forms develop and subsequently liberate merozoites to infect red cells and start new generations of patent parasites, so that there probably are in these infections periods of true freedom from parasitaemia separating the patent intervals

The duration of parasitaemia is variable It is probably shortest in the case of falciparum infections Direct measurement in limited series in America showed that with one strain of this parasite the mean frequency was 222 days, the longest observed being 480 days, whilst with another strain the mean was 280 days with a maximum of 503 days, but it must not be taken that these limited series include the extremes which may be found in nature The normal duration of vivax infections is probably of the order of two and a half or three years, though, again, some may persist for a considerably longer time *P malariae* probably usually persists for considerably longer there are many records of long duration and one of persistence for 32 years There is little knowledge of the longevity of ovale infections

The pattern of relapse in vivax infections may also differ from that described There are certainly many widely differing strains of the parasite and they appear to be divided into two groups In one there is a marked tendency to prolonged latency, sometimes as a greatly prolonged incubation period, and in the form of an interval of the order of 30 or 40 weeks between the original attack and the first relapse, in the other there is a more random distribution of relapses resembling the pattern found in falciparum infections

Gametocytes are a product of the asexual forms appearing in the blood stream and hence it is probable that their appearance is always to some extent delayed after first parasitaemia In vivax infections, however, the delay is very slight, and for practical purposes it may be taken that sexual and asexual forms appear in the blood at roughly the same time, each crop of asexual parasites in turn producing gametocytes so that parasitaemia is usually synonymous with gametocytaemia In falciparum infections the position is very different Gametocytes do not appear in the blood

until 10 to 12 days after the first appearance of asexual parasites they are not infective for 2 to 4 days after their first appearance and they persist in the blood for considerably shorter times than do the trophozoites, tending to occur in waves separated by intervals in which they may not be present The total duration of gametocytaemia is therefore considerably less than of parasitaemia They are most numerous during the early stages of the infection when they may well exceed 1,000 per mm³ for several weeks, but thereafter they decline in numbers and in long-established infections 10 per mm³ is a normal figure and 100 per mm³ very rare

The infectivity of the gametocyte to mosquitoes is roughly but not absolutely related to the numbers in the blood, there being some inexplicable cases where density has been high and where it has been impossible to infect mosquitoes from them During the initial stages of infection, however, 50 per cent or more of susceptible mosquitoes fed on a case usually become infected, though in the later stages this may diminish to 10 per cent or even less There does, however, appear to be considerable variation between strains of parasite in this respect, as there is *also in the susceptibility of different anophelines*

For the purposes of analysis these characteristics must be rendered in some numerical form, and although description of one case in this way may be very difficult it is possible to devise a reasonable form when considering numbers of cases whose infections were derived at different times The simplest expression is the mean duration of parasitaemia, or numbers of days on which parasites appear in the peripheral blood regardless of whether they are consecutive or not For analytical purposes it is often more convenient to use the reciprocal of this, or the probable proportion of cases which will become negative during a period of one day, and this form is adopted in the analyses presented here It may be used to represent a recovery rate either from parasitaemia or from gametocytaemia, but the case is slightly more difficult in considering infectivity because an individual is not wholly infective on any day in the sense that he infects all mosquitoes feeding on him Properly there should be a double representation

of a duration of gametocytaemia together with a figure representing the mean proportion of anophelines feeding on the individual during gametocytaemia which become infected This rather complicated double figure can, however, be condensed back into a single one if it is remembered that it represents the compound, this rather simplified form is used, a recovery rate being expressed for infectivity just as for gametocytaemia or parasitaemia The actual values of these recovery rates differ with species of parasite and, indeed, with each strain, but on a review of natural happenings it has seemed reasonable to adopt figures considered as representative of many natural conditions for use when numerical examples have to be worked For this purpose it has been assumed that the mean duration of parasitaemia in a non-immune person is of the order of 200 days and of infectivity about 80 days, giving recovery rates respectively of 0 005 and 0 0125

Epidemiological happenings are inevitably greatly influenced by the occurrence or non-occurrence of superinfection Infection with *P vivax* confers an early immunity against superinfection or reinfection with that particular strain of parasite, without at first a heterologous immunity against other strains Repeated infection with different strains, however, builds up a heterologous immunity which eventually becomes general and the individual becomes resistant to infection with the species Superinfection with the same strain of parasite is rarely, if ever, possible though it may occur with other strains of the parasite before firm immunity is acquired The picture in falciparum malaria is similar in principle though different in degree Stimulation of immunity is much slower and a patient has been superinfected experimentally on three occasions with the same strain of parasite However, a homologous immunity to the original strain does eventually develop, restricting the possibility of superinfection except by other strains, and ultimately resulting in considerable resistance to further infection with any strain The possibility of repeated superinfection with different strains of parasite has been amply demonstrated in monkey malaria, in nature there are probably a number of strains and species of human parasite transmitted at any one moment, and natural happenings cannot be explained

except on the basis that *superinfection is a common* occurrence in the field The subject is chiefly of importance in attempting to understand happenings in places where malaria is hyperendemic and *P falciparum* predominates In such places it is rational to assume that certainly during the first few years of life and perhaps in some places for much longer times the occurrence of one infection with falciparum makes no material alteration to the probability of another during its course, and that fresh infections during this time are marked by a fresh onset of parasitaemia materially unaffected by the previous one

STAGES IN THE MOSQUITO

There was for long considerable doubt about variation in the susceptibility of anophelines until the answer was established by experiments in which different species of anophelines were fed simultaneously on the same patient, and the proportion in each group which became infected was noted The position is very *complicated as the susceptibility of any anopheline varies with the* species of parasite to which it is exposed and indeed with the strain of parasite, so that one mosquito may be quite susceptible to *P falciparum* derived from one country and *resistant to* infection with a strain originating elsewhere In some cases refractoriness is virtually complete and in this context the species can be considered as not being a vector, but where there is any material susceptibility the range of variation is not great and probably has a much lesser influence on transmission than other variables such as longevity and man biting habit Assuming that infection is established in the mosquito, the time taken for the completion of sporogony to the stage of invasion of the salivary glands by the sporozoites is dependent on temperature, while the weight of evidence shows that atmospheric conditions such as humidity are of little importance, though they may affect the mosquito's expectation of life and so prevent completion of the cycle There are minimum temperatures below which development is indefinitely retarded, 19° C for *P falciparum* and 15° C for *P vivax* High temperatures are lethal to the parasite, the proportion surviving decreasing rapidly at temperatures over

32° C Within the limits thus set the rate of development is a function of temperature Collation of all the available evidence suggests that it is in the form shown in Figure 1 for *P falciparum* and *P vivax* Data are insufficient on which to present even a tentative curve for the other two parasites The minimum temperature permitting development of *P malariae* is probably of the same order of that for *P vivax*, though the time of development of the former is probably very much longer

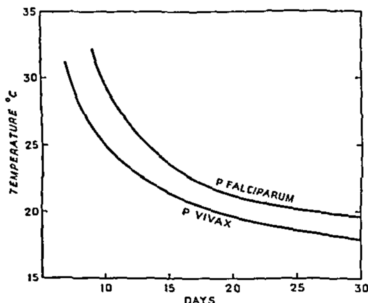


Fig 1 The period of extrinsic development of *P falciparum* and *P vivax*

The invasion of the salivary glands by sporozoites is a necessity for infectivity but is by no means synonymous with it, a proportion of failures being invariable in experimental inoculation and more common in falciparum infections than in vivax The mosquito is not infective unless sporozoites are present in the duct as well as the cells of the gland Infectivity is then related to the numbers of sporozoites present In experimental work, where infections are usually heavy, a relationship has been shown and mosquitoes with over 50 oöcysts on the stomach convey infection to about half the people they bite, whilst those with smaller numbers infect very much lower proportions There is no available experimental

evidence on the infectivity of mosquitoes with very small numbers of oocysts, such as are usual in many permanently malarious areas, but reasonable extrapolation from experimental data suggests that the proportion of sporozoite-infected mosquitoes which actually convey infection must in many of these places be very small Even when the infection is heavy, repeated biting depletes the numbers of sporozoites in the salivary glands and thereby causes a progressive loss of infectivity Sporozoites are also thought to undergo degeneration after some time and to become non-infective, and it has been asserted that a considerable proportion of sporozoite-infected mosquitoes in nature show degenerated sporozoites only, though it is difficult to check the validity of this statement In general it must be taken that infection of the salivary gland is not necessarily synonymous with invariable or even with usual infectivity on biting, and since direct evidence is unobtainable the collection of indirect data on the proportion of mosquitoes which are actually infective is fully justifiable

Completion of sporogony to the development of sporozoites is dependent to a minor extent only on the viability and nutrition of the parasite itself, because most infections in the mosquito run to completion if the mosquito survives The prospect of survival of the mosquito is incomparably the most important determining factor, and although it is one of the most important aspects of epidemiology, it has received extraordinarily little study and the known efforts at measurement are very few There are two aspects the pattern of mortality and the mortality rate The pattern is in principle probably much the same for most animal species Immediately after emergence the mosquito is delicate and exposed to considerable hazards so that the death rate in the first few hours or possibly the first day or two is probably high Thereafter there is a long period during which death from natural causes is uncommon until a terminal age is reached when it becomes increasingly frequent The numerous studies of the maximum time of survival of anophelines maintained with care in insectaries show that this terminal stage is not reached until two, three or even more months after emergence Mosquitoes in nature are, however, exposed to considerable risk and most

deaths are undoubtedly due to causes other than degeneration and lack of viability The great bulk of the population in nature is in an age period when viability is more or less constant and death is generally due to hazard of climate, natural enemy or other external circumstances falling almost equally on all It is therefore rational to look on mosquitoes as subject to a risk of death within any limited period which is independent of their age at the time It is known that this is not a precise representation of happenings, but experience with many colonies, some of which have been kept for this specific purpose, shows that it is a very near approach It can be used with confidence unless the group of anophelines concerning which conclusions are to be drawn is a very young one, mostly less than a couple of days old

It is convenient to express mortality as a probability of survival rather than as a probability of death within any given period The form here adopted is a probability of survival through one day, which is given the symbol p in the text and in all expressions Thus a probability of survival of 0 95 means that on the average 95 per cent survive through one day, and the daily mortality is 5 per cent

On this understanding it is possible to give fairly simple expressions for probability of survival and for expectation of life which, though not precisely correct, are sufficiently so for all normal purposes

1 The probability of surviving through n days is p^n

2 The expectation of life is

$$\frac{1}{-\log_e p} \quad \text{or} \quad \frac{1}{-2\ 303 \log_{10} p}$$

3 The expectation of life after survival through n days is

$$\frac{p^n}{-\log_e p}$$

These identities remain substantially true whatever the age of the mosquito when it is first observed and may be applied to any population whatever its composition The natural logarithm ($\log_e$) is here introduced and is used consistently hereafter, it is the same as the ordinary or Napierian logarithm multiplied by 2 303 and like any logarithm is itself negative when it refers to a

fraction. Table 1 gives values of p^n and $-\log_e p$ covering representative ranges of values of p and n for which the expression may commonly be used. Interpolation for intermediate values of p may easily be made by graphical means or by quite simple working

TABLE I

Values of p^n and $-\log_e p$

Value of p —	0 95	0 9	0 85	0 8	0 75	0 7	0 65	0 6	0 55
p^8	0 663	0 430	0 272	0 168	0 100	0 058	0 032	0 017	0 008
p^9	0 630	0 387	0 232	0 134	0 075	0 040	0 021	0 010	0 005
p^{10}	0 599	0 349	0 197	0 107	0 056	0 028	0 013	0 006	0 003
p^{11}	0·569	0 314	0 167	0 086	0 042	0 020	0 009	0 004	0 001
p^{12}	0 540	0 282	0 142	0 069	0 032	0 014	0 006	0 002	
p^{13}	0 513	0 252	0 121	0 055	0 024	0 010	0 004	0 001	
p^{14}	0 488	0 229	0 103	0 044	0 018	0 007	0 002		
p^{15}	0 463	0 206	0 087	0 035	0 013	0 005	0 002		
p^{16}	0 440	0 185	0 074	0 028	0 010	0 003	0 001		
p^{17}	0 418	0 167	0 063	0 022	0 007	0 002			
p^{18}	0 397	0 150	0 054	0 018	0 005	0 002			
p^{19}	0 377	0 135	0 046	0 014	0 004	0 001			
p^{20}	0 358	0 121	0 039	0 011	0 003				
$-\log_e p$	0 051	0 105	0 162	0 223	0 288	0 357	0 431	0 511	0 598

Note The fact that $\log_e p$ is a *positive* number must be borne in mind

The further distribution of infection after sporozoites have developed depends on the expectation of life of the mosquito, an expression for which is given above, and the frequency with which it bites man. This latter is a compound of two characteristics: the frequency of feeding and the choice of host. The frequency of feeding is probably tied in all anophelines to the rate of ovarian development, which is in turn largely dependent on temperature, but within the temperature range at which malaria is commonly transmitted being often once in two days, or on the average 0 5 times per day. The choice of host varies greatly with the species of mosquito and the opportunity available to it, many species having a marked predilection for one type of host which they select if reasonably available, taking other hosts only in the absence of preferred food. A few anophelines are anthropophilic in that they select man as a host if possible, and this group includes some of the most potent malaria vectors such as *Anopheles gambiae*,

A funestus, A minimus minimus, A sacharovi, A labranchiae, and *A darlingi* throughout most of their natural range Others have a distinct preference for lower animals, some never biting man and so not coming within the picture of transmission of malaria There are a number which will take man as a second alternative, normally feeding only occasionally on him but being prepared in the absence of the preferred host to take a preponderant diet of human blood They may thus be attracted to man or to animals according to their availability Many of the important malaria carriers are within this group, their importance turning largely on the frequency with which they select man under any given set of circumstances Included in this group are such important carriers as *A minimus flavirostris, A hyrcanus sinensis, A maculatus A culicifacies, A stephensi, A superpictus, A atroparvus, A quadrimaculatus, A albimanus, A aquasalis* and a number of others The biting habit is an extremely important characteristic and can only be determined by local studies utilising the precipitin test It is worth remembering, however, that the only information the malariologist requires is whether human blood is selected or not, and that considerable elaboration of technique in order to determine the precise nature of other sources of food is quite unnecessary

The cycle of transmission is described in full detail and with full documentation in —

Boyd M F *Malariology* Chapters 25 and 26, Volume I, 551–697 Philadelphia and London W B Saunders Co, 1949

and excellently but more briefly in —

Russell, P F West L S & Manwell, R D *Practical malariology* Philadelphia and London W B Saunders Co 1946

Some of the special aspects here described can be studied in —

Macdonald G The analysis of malaria parasite rates in infants 1950, *Trop Dis Bull*, 47 915–938

Macdonald, G The analysis of the sporozoite rate 1952, *Trop Dis Bull* 49 569–586

Eyles D E & Young, M P The duration of untreated or inadequately treated *Plasmodium falciparum* infections in the human host. 1951, *J nat Malar Soc*, 10, 327 336

JEFFERY, G M & EYLES, D E The duration in the human host of infections with a Panama strain of *Plasmodium falciparum* 1954 *Amer J trop Med*, 3, 219–224

JEFFERY, G M & EYLES, D E Infectivity to mosquitoes of *Plasmodium falciparum* as related to gametocyte density and duration of infection 1955, *Amer J trop Med*, 4, 781–789

and two full field surveys based on the present approach are described in —

DAVIDSON, G & DRAPER, C C Field studies of some of the basic factors concerned in the transmission of malaria 1953, *Trans roy Soc trop Med Hyg*, 47, 522–535

DAVIDSON, G Further studies on the basic factors concerned in the transmission of malaria 1955, *Trans roy Soc trop Med Hyg*, 49, 339–350

CHAPTER III

QUANTITATIVE ASPECTS OF TRANSMISSION

INTERACTION OF TRANSMISSION FACTORS

REPRODUCTION RATES

A NUMBER of concepts and mutual relationships can be derived from the chain of transmission which has been described Their derivation is by mathematical techniques which are set out in detail in Appendix I but which are explained here in a colloquial form The most important is the concept of a reproduction rate One may imagine an individual suffering from falciparum infection who is infective to all the mosquitoes which feed on him during 80 days (or half of those which feed on him for 160) If 10 bite each day he originally infects 800 mosquitoes These might have a probability of survival through one day of 0 9, if the temperature were such that the extrinsic cycle lasted 12 days, 28 per cent. of these (Table 1) would survive to the development of sporozoites and they would have a subsequent expectation of life of 10 days If the mosquito were entirely anthropophilic, feeding once every 2 days on man, the survivors would on the average each convey the infection to 5 people Through this mechanism 1,120 infections might be distributed in the population from the primary case In the immediate context it is no matter that a number of these infections would be nullified by overlapping on the same individual Obviously nothing approaching such a rate of multiplication could go on unchecked for long and there are three brakes on multiplication which eventually restrain it They are the development of immunity in a population which restricts the duration of infectivity the existence of previous infections in individuals receiving infective bites which may not therefore apparently produce new cases of the disease, and the occurrence of superinfection in the mosquito which may have previous infections so that subsequent ones do not materially increase its infectivity

These factors together reduce the gross reproduction rate to a net one which may be much lower Should this fall below one successive generations of cases would be smaller than their predecessors and the disease would disappear, should it be greater than one, successive generations would increase and the disease would mount in the population Obviously the object of all control is to keep the reproduction rate below one so that successive generations decrease in size and the disease disappears Since in the last resort when malaria is in process of disappearing the gross and net reproduction rates are the same it can be said from the start that the object is to reduce the gross reproduction rate below one

THE CRITICAL LEVEL

The idea of a critical level follows from this It is not necessary to eliminate transmission completely in order to get disappearance of the disease but only to reduce it below some significant level after which the disease will decrease indefinitely This is a most important concept in epidemiology, particularly in that of malaria, and explains the occurrence in some parts of the world of anophelism without malaria, transmission having occurred at such a low rate that the disease automatically extinguished itself

THE SPOROZOITE RATE

This depends on the chance of the mosquito taking infective feeds, on the period of the extrinsic cycle, and on the mortality rate of the mosquitoes, in a manner illustrated in Figure 2, which is an illustration of expression (7) in Appendix I The graphs have been developed as a result of theoretical working which has been well checked in the field and shown to be substantially correct In the most malarious conditions of Africa the sporozoite rate is usually of the order of 10 per cent, which represents a survival rate of about 0 95, that is to say a 5 per cent daily mortality, a 12-day extrinsic cycle, and about a 1 per cent chance of a mosquito biting an actually infective person on any particular day, for in these conditions in Africa the prevalence of infective people is reduced by the occurrence of immunity In parts of India where

malaria is transmitted by *A culicifacies* very much lower sporozoite rates of the order of 0 1 per cent are often recorded In an extensive series of surveys made by Russell and his co workers in Madras the rate was 0 064 per cent , this was attributable to a 22 5 per cent daily mortality of the mosquito which, on the average, took only 1 out of 40 of its feeds on man an extrinsic cycle for *P vivax* of about 9 days and a gametocyte rate in the population of about 13 per cent

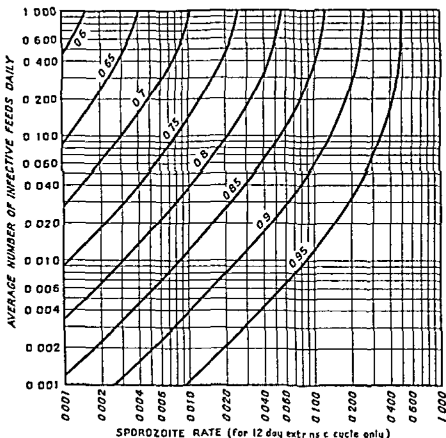


Fig 2 The sporozo te rate in relat on to anopl eline longevity and the frequency of infective feeds Each graph refers to a d fferent probability of survival through one day wh ch is shown on it (Redrawn from *Trop Dis Bull* 1952 49 569)

THE PARASITE RATE

Having analysed the relationship of the sporozoite rate to the gametocyte rate, the next point is to examine the parasite rates

which would be given by a constant inoculation rate. The subject is examined mathematically in Appendix I and illustrated in a series of graphs in Figure 3. These show how the parasite rate in infants might be expected to mount with passing time and increasing probability of infection according to the inoculation rate to which they are exposed. In each case the curve mounts to a plateau. Where the inoculation rate is lower than the recovery rate this plateau is below the level of 100 per cent. infections.

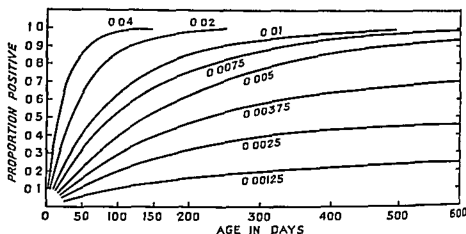


Fig 3. The infant parasite rate in relation to inoculation rate. Each graph refers to a given daily inoculation rate shown on it.

In other cases the parasite rate rises rapidly to 100 per cent. and subsequently remains at that level, the majority of individuals actually suffering from two or more concurrent infections. These theoretical graphs have been checked against similar curves observed among infants in nature, an example being shown in Figure 4.

EPIDEMICS

In nature the parasite and sporozoite rates are dependent on each other. An increase in the parasite rate automatically increases the sporozoite rate, which in turn increases the parasite rate, and so on until the brakes on multiplication, the occurrence of superinfection in man and the mosquito, bring it to an end. The next process in analysis is to examine the form of happenings when both the parasite rate and the sporozoite rate are allowed to vary in a manner dependent upon each other. Assuming for the

sake of illustration that there has been some mild malaria in a community and thus a reservoir from which the disease can arise, and that transmission is abruptly increased, an epidemic results. The mathematical expression of an epidemic is extremely complicated and for long defied working. The complication arises from the influence of the incubation period, or actually a longer period than that usually known by this name, the interval between the occurrence of infective gametocytes in a case and their appearance in an infective form in a secondary case derived from it. In order to indicate this enlarged scope it is described henceforth as the incubation interval. Neither in fact nor in theory do

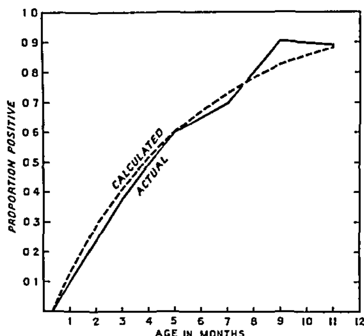


Fig 4 Actual infant parasite rates with a fitted curve Actual data are from records in Kenya by Garnham Observed and calculated values are —

Age	*Median age, corrected Days*	*Proportion positive*	
		Actual	*Calculated*
0– 1 month	20	0·095	0·122
2– 3 months	82	0·39	0·414
4– 5 "	142	0·60	0·064
6– 7 "	203	0·70	0·734
8– 9 "	264	0·90	0·821
10–11 "	325	0·89	0·880

(*Trop. Dis. Bull*, 1950, 47, 929)

cases occur during an epidemic in the form of a smooth curve which might be expressed by a single formula, but they come as a series of generations of cases, the numbers of which in each generation require separate description Expressions for them are given in Appendix I, and there is a separate and somewhat simplified description in Chapter V which deals with the special case of epidemics arising from small origins such as might be a problem during eradication programmes Happenings may be outlined as follows if a pre existing equilibrium of transmission is disturbed by an increase in transmission, there will be no

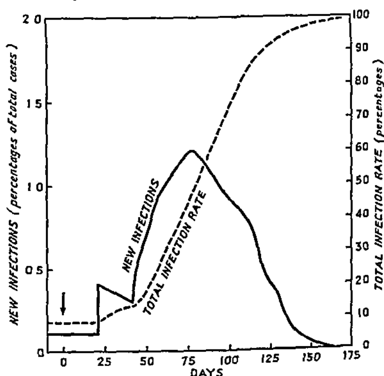


Fig 5 Epidemic curves showing the proportion of persons infected and the incidence of new infections The curves are diagrammatic illustrating the chain of events following an increase in transmission at zero days indicated by an arrow The time scale and the height the two curves rise would depend on the value of several variables

further multiplication of cases for the duration of one incubation interval, during which time transmission will be in progress but not complete in the form of manifest cases During the second incubation interval there is an increase of cases but they arise from a reservoir of gametocyte carriers which was static throughout

the interval during which the anophelines were acquiring their infection If the start of the increased transmission was sharply defined the daily access of new cases would be approximately the same throughout this second incubation interval, a fact which is represented in many natural epidemic curves by a curious step or *hesitation at the beginning of the epidemic curve* In the third

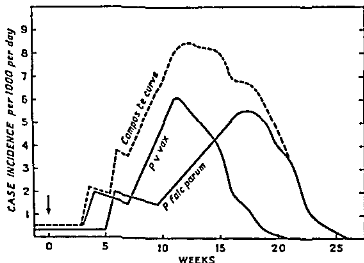


Fig 6 Separate and combined curves of epidemic due to *P falciparum* and *P vivax* The composite curve represents an epidemic as it is usually seen in nature Factors precipitating the epidemic are assumed to operate from zero time, indicated by an arrow

incubation interval cases arise from a gametocyte reservoir in the previous one which was steadily increasing, with the consequence that the daily number of new cases increases progressively throughout this interval In the fourth and subsequent intervals this multiplication is exaggerated There result epidemic curves of the type shown in Figure 5, one of which refers to the access of new cases and the other to the increasing proportion of the population which is infected, and of course including both new and old cases

The incubation intervals in vivax and falciparum infections are very different, due to the slightly longer period of the extrinsic cycle in falciparum infections, and to the considerable prolongation of the period before infective gametocytes appear in the blood in the latter disease

The difference in the incubation interval greatly influences the timing of epidemics of the two diseases Most natural epidemics consist of mixed outbreaks of vivax and falciparum malaria and in reality there are two separate epidemics which together form a combined curve like the upper one in Figure 6 This may be compared with actual happenings in nature In every one of the local Ceylon epidemics of 1934/35, and in most subsequent ones one can trace the same general form Almost all natural epidemics do in fact consist of two separate curves, as has been shown, and the occurrence of a very abrupt start, the preliminary appearance of *P vivax* and the subsequent appearance of *P falciparum* with a high mortality are accepted features With this verification it has been possible to fit theoretical curves to the actual curves of a major epidemic in Ceylon, as in Figure 7, and from this process of fitting find the order of events, the amount of multiplication of mosquitoes necessary to produce such a catastrophe

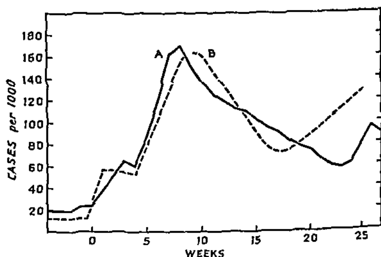


Fig 7 An actual epidemic curve from the Deduru Oya Basin Ceylon in 1934 35 (A) and a synthetic curve (B) built to resemble it In this latter each fresh infection has been credited with 1 8 attendances in order to bring the total of attendances in the two occurrences to the same figure The final increase in the synthetic curve is due to late appearance of *P falciparum* infect ons (Redrawn from *Trop Dis Bull* 1953 50 875)

EQUILIBRIUM

Epidemics reflect two factors new cases and the parasite rate The latter mounts from the start of the epidemic to achieve a

plateau, which may be at or below 100 per cent of the population, as in the case of the infant parasite rate It is represented by expression (26), given in Appendix I, which cannot be easily checked in nature because when this steady stage is reached immunity sets in, alters the value of one of the factors involved—the duration of the disease—and invalidates direct comparison The expression might therefore remain one of academic interest except that it can be used in subsequent examination of the stability of equilibrium, a very important concept which may be illustrated by a mechanical analogy no engine however well governed runs perpetually at the same speed, an increase of the load on it produces some slight decrease in speed though this may later be adjusted by the governing mechanism Now imagine two engines one of which is fitted with a reasonably efficient governor which keeps it running at roughly the same speed whatever the load that may be put upon it, and another which has an extremely inefficient governor so that with variation of the load or the amount of fuel supplied the speed shows great divergences from the normal The speed of the first is fairly stable and of the second unstable Such a mechanism happens in any insect-borne disease according to the efficiency of the brakes mentioned earlier The brake of cancellation of infections falling on already infected people is always the same The brake to multiplication applied by the probability that infections would fall on mosquitoes which are already infected will vary very greatly with the characteristics of the mosquito and the probability of its taking more than one infective feed Theory suggests that the greater the probability of the mosquito biting man, in the form of its biting habit, choice of man, and length of life in which to bite, the greater will be the overlap of infections in the mosquito and the more efficient the governing mechanism, resulting in a much more stable epidemiological condition with less tendency to vary from the mean It is in exactly this characteristic of degree of variation about the mean that natural conditions differ so markedly from each other In some places malaria repeats itself annually with astonishing regularity, and in parts of the perennially warm tropics the disease shows very little variation over several years

However, in other places, such as northern India, parts of Pakistan and in Ceylon, the variations from year to year are extreme In some places there is a periodic variation with a cycle of about 8 to 20 years, but apart from this good and bad years follow each other in an irregular manner Examination of the vectors of *malaria shows that these two characteristics do in fact depend* on the longevity and the biting habit of the mosquito as theory had indicated they would

THE EFFECT OF ACQUIRED IMMUNITY

There are several actual or assumed types of immunity certainly there is some degree of natural genetic immunity to *P vivax* amongst some Africans whether still resident in that continent or not It has been postulated, though on evidence still inadequate, that there is some passive transmission of maternal immunity to the infant which may persist for some months and it has been proven in animals and postulated in man that there may be a dietary immunity amongst those living on an exclusive milk diet which prevents—or perhaps may retard—the growth of the malaria parasite The present concern, however, is solely with acquired immunity Experimental inoculation shows *that infection* with *P vivax* confers a homologous immunity preventing super infection or subsequent reinfection with parasites of the same strain though not necessarily with other strains of the same species A small degree of heterologous immunity to other strains is produced and repeated infection with several strains may ultimately produce a firm heterologous immunity to all In the case of *P falciparum* the general picture is somewhat similar, but the degree of immunity conferred is considerably less

The clear-cut effects of infection with particular strains cannot be observed in the field, but only the general effect of inoculation with parasites of two or more species and of an unknown number of strains of each The subject has been most studied in areas where malaria is intense and roughly perennial and where *P falciparum* is the predominant parasite In such circumstances there can be little doubt that superinfection that is the imposition of a second infection on a first before it has died out commonly occurs

Events in such places are illustrated in Tables 2 and 3 The sequel to infection in the youngest infants under about 6 months of age is a moderately intense parasitaemia averaging perhaps 3,000 parasites per mm³ Amongst slightly older children, between 6 and 12 months, the sequel is a more intense parasitaemia averaging perhaps 6,000 to 10,000 per mm³. There have been considerable discussions on the reason for this apparent increase in susceptibility, but the evidence on which to distinguish between the results of loss of passively transferred immunity, dietary change, and the contrast between the effects of the single and multiple infection is quite inadequate Typically, intense parasitaemia continues in the children up to the age of 2 or 3

TABLE 2

Changes in parasite density in relation to duration of period of exposure to infection

[Data from Christophers S R (1924) *Indian J med Res*, 12, 273]

Period of residence	Percentage infected	Average parasites per mm³
Under 1 year	74	4 688
1 year	92	10 659
2 years	100	7,124
3	87	1 082
4	89	726
5 ,	94	810
6–10 years	96	1 070

About this time a crisis occurs, immunity becomes considerably reinforced, and the parasite density decreases to about one-tenth of its previous value Throughout subsequent childhood intermittent parasitaemia occurs, children may show high parasite densities occasionally and probably following a fresh infection, more usually they show few parasites in the blood, and there may be many days on which none can be found by usual techniques Under these conditions virtually all the children are infected with malaria and the frequency with which they show parasites in their peripheral blood reflects the intensity of infection and the number

of concurrent infections, new and old, which they may have As they grow older their immunity grows firmer and more general the frequency of periods of freedom from parasitaemia increases and in consequence the general parasite rate of the older group and of adults decreases

This is the common picture of the development of immunity seen in the field, but there is another aspect which is less frequently remarked upon but which from the communal point of view is probably much more important The ability to restrain the production of gametocytes comes much earlier than that to restrain schizonts In epidemics amongst non immune people gametocytes are extremely common, appearing in all age groups and the majority of infected persons show them In places where malaria is endemic but at a low level of transmission gametocytes are also frequent in all age-groups, occurring in about 30 to 40 per cent of those with asexual *P falciparum* parasites, but in places such as those now described where transmission is continuous and intense there is a very marked restriction of heavy gametocytaemia to the youngest age group, and the peak of gametocytaemia is passed long before that of parasitaemia as a whole is reached Relatively dense infestations with gametocytes become restricted to the first year of life, to the first 6 months or even in one extreme case recorded by Davidson, and recorded in Table 3, to the first 3 months of life In this example the critical fall in the density of schizonts did not occur until after 2 years of age

The presence of sporozoites in an anopheline's salivary gland is not synonymous with infectivity to man any more than gametocytaemia is synonymous with infectivity to mosquitoes In both cases infectivity depends on a number of factors, extremely important ones being the number of gametocytes in the original host and the number of sporozoites developed from them The rarity of heavy gametocyte infestations in all but the very youngest who are themselves few in numbers, greatly reduces the reservoir of infective cases available to the anopheline The very low gametocyte densities that prevail in young and old alike also reduce the average density of infection in such anophelines as

become infected, and thereby reduce their infectivity to man The effect of this dual reduction in infectivity in the two stages of infection of the mosquito and of man is immense In the survey just referred to only about 4 per cent of feeds on man by anophelines caused infection of the anophelines, though schizonts were present in about 50 per cent Moreover only about 1 in 20 bites by mosquitoes with sporozoites in their glands resulted in infection of the individual bitten

TABLE 3

Relation of density of falciparum schizonts and gametocytes to age in a community subject to holo-endemic malaria

[Data from Davidson G (1955) *Trans roy Soc trop Med Hyg* 49 339]

Age	Percentage positive	Mean density of schizonts per mm³	Percentage showing gametocytes	Percentage showing over 100 gametocytes per mm³
2 weeks–	66	7 000	41	13
4 months–	83	15 000	44	3
6 months–	90	13 000	51	2
9 months–	99	13 000	44	3
12 months–	98	10 000	44	2
18 months–	98	11 000	36	2
24 months	97	5 000	35	0
5 years–	94	2 000	28	1
10–15 years	88	1 000	15	0
Over 15 years	31	100	5	0

The working of this process constitutes a very delicately balanced governing mechanism If, in a community subject to fairly constant transmission, the frequency of transmission is increased there results a restriction of gametocytaemia and particularly of high gametocyte density to ever younger and smaller age groups This in turn limits transmission, and brings it back to near its original value, the net effective reproduction rate remaining much the same and usually at a value of about 1 2, just above the critical level at which transmission would end Both before and after the change there is therefore a state of balance in which transmission is very closely related to the history of immunity in the population and the latter's ability to

bear the disease The chief differences after the increase are an earlier likelihood of infection in infants, an earlier peak and crisis in the initial period of high gametocytaemia, and probably some adjustment in the immunity of older children and adults, further restricting the periods in which they show gametocytes and asexual parasites in the blood

In places where malaria is irregular in occurrence there is no marked limitation of susceptibility to the youngest age groups the extent to which it occurs depending on the length and regularity of the period of transmission There may grow up in such areas considerable groups of people with no resistance to the disease Should an epidemic occur the multiplication of cases is for some time unfettered by immunity, which takes time to develop, and the net effective reproduction rate may reach very much higher levels than are ever seen in places of continuous transmission Immunity, however, ultimately develops and restriction of gametocytes develops fairly early It appears in response to an unrestrained stimulus which far exceeds the normal for the area and the consequent immunity is considerably more than is necessary to limit the normal degree of transmission As a result there may be, after the epidemic, an abnormal reduction of the disease which, under some conditions, goes to the extent of achieving local elimination In this way epidemics may be followed by an apparently spontaneous disappearance of the disease, as has happened many times in northern Europe and elsewhere It is probable that severe epidemics such as those once well known in northern India are often followed by local elimination in a considerable proportion of the villages which were affected, but that these are interspersed with others in which some residual transmission remains In the immediately following years there may be a patchwork condition with transmission in some areas and none in others, a happening well known in Holland Persistence is most likely in those places where communal immunity is most rapidly diluted by the birth of new infants or arrival of other immigrants and in the Dutch example continuation was in those places where there were most children After a period of quiescence the disease spreads slowly over the

countryside again and flares up ultimately into an epidemic to be again followed by the same sequence of events

Just as this form of immunity plays a very considerable part in limiting the influence of any increase in malariogenic conditions, so does it play an important part in limiting the effect of control measures Any decrease in transmission in a place where immunity is playing an important role inevitably results in a decrease in the immunity and a relative increase in the gametocyte reservoir, restoring the net reproduction rate to very much the same level as prevailed beforehand This balancing mechanism continues and the results of an insufficiently thorough control campaign may be most disappointing, marked by considerable decreases in anopheline prevalence and in the inoculation rate as recorded by *entomological means,* but by *only small changes in the human* picture There are fortunately, however, limits to the reduction in resistance, and a time comes when a further decrease in transmission is not matched in this way The net effective reproduction rate is then brought quite abruptly below its critical level of 1 0, and malaria is on its way to elimination in that locality Such elimination however, is likely to be at first local and patchy in distribution If control were to be stopped reinvasion would be probable, though not perhaps in the dramatic form which has been very freely forecast but has not been seen in areas in Central Africa where control has been discontinued A relatively slow dissemination of the disease, a multiplication of foci and their coalescence again to form a uniform endemicity represents more accurately what has usually been seen The prevention of such recrudescence demands active work to search out and eliminate the residual foci, turning the local elimination into a more ample regional eradication throughout an area which it is economically possible to protect against further invasion

The influence of immunity on restriction of gametocyte output is analysed in —

SCHUFFNER W A P Two subjects relating to the epidemiology of malaria 1919 reprinted 1938, *J Malar Inst India,* 1, 221–256

MACDONALD, G Community aspects of immunity to malaria 1951 *Brit med Bull*, 8, 33–36

The mathematical aspects are developed in —

MACDONALD, G The analysis of infection rates in diseases in which superinfection occurs 1950, *Trop Dis Bull*, 47, 907–915

MACDONALD, G The analysis of malaria parasite rates in infants 1950 *Trop Dis Bull*, 47, 915–938

MACDONALD, G The analysis of the sporozoite rate 1952, *Trop Dis Bull*, 49, 569–586

MACDONALD, G The analysis of equilibrium in malaria 1952, *Trop Dis Bull*, 49, 813–829

MACDONALD, G The analysis of malaria epidemics 1953, *Trop Dis Bull*, 50, 871–889

MACDONALD, G The measurement of malaria transmission 1955, *Proc roy Soc Med*, 48, 295–301

CHAPTER IV

EQUILIBRIUM

BACKGROUND

According to the argument which has been developed any great difference in the average number of feeds taken on man between mosquito species should have material effects on the basic reproduction rate and on the stability of malaria A couple of examples will illustrate the degree of difference between notorious vectors, both responsible for producing high endemicities In Madras the probability of survival of *A culicifacies* through one day has been measured as 0 775, the expectation of life is about 3 8 days, and in the same surroundings the probability of its feeding on man in one day is about 0 0125, it follows that the chance of the mosquito taking a bite on man during a normal lifetime is about 0 0475 It has similarly been shown that the expectation of life of *A gambiae* in East Africa is about 13 days, and the probability of its feeding on man on any one day 0 5, the chance of feeding on man during a normal lifetime is therefore about 6 5 some 136 times as great as for *A culicifacies*

There should then be a radical difference between malaria in East Africa and in Madras In the former, a brake should operate to make the human infection rate relatively unresponsive to changes in transmission factors, whilst in the latter it should respond to them in an exaggerated way This is in fact the primary distinction between the two epidemiologies, malaria in equatorial Africa is characterised by an absence of epidemics and sluggishness in its variations in Madras by epidemics, appearances and disappearances, and a general mercurial nature The comparison can be carried much further by a mathematical analysis of expected critical densities and of the effect of changes in mosquito density, probability of survival, period of the extrinsic cycle, and biting habit on the human infection rate The mathematical forms of these influences are worked out in Appendix I and some of their implications may be put verbally

They suggest that the degrees of equilibrium seen in nature should make a continuous series, of which the two extremes can be termed stable and unstable malaria and which mathematical analysis alone indicates should have the following characteristics

STABLE MALARIA

Determining causes Transmission by a vector with a frequent man-biting habit, with a moderate to high longevity, at a temperature favourable to rapid completion of the extrinsic cycle

Anopheline density needed to maintain transmission Very low, of the order of 0 025 bites on the average person each night, or even less

Endemicity Anophelism without malaria would probably be unknown Low to moderate endemicities would probably be found, but very high endemicities would be common

Seasonal changes Reduction of temperature below about 15° C would stop transmission, a seasonal epidemic occurring during the warm weather, starting at a relatively low temperature and only terminated by low temperature Seasonal conditions unfavourable to breeding or to prolonged adult survival would not be likely to terminate transmission completely unless the reduction of breeding was extremely marked

Fluctuations in incidence Fluctuations other than normal seasonal changes are not likely to be marked except in the presence of obvious causes Epidemics would be very unlikely to occur

Effect of cool weather Transmission is likely to continue at almost all temperatures permitting completion of the extrinsic cycle, and therefore tends to occur at high altitudes and latitudes within the range of the vector In cool weather the sensitivity to changes in probability of mosquito survival becomes exaggerated so that marked fluctuations and epidemics might occur in such places Sensitivity to changes in anopheline density remains materially unaltered by cool weather

Immunity of population The regularity of transmission is likely to ensure a stable immunity, varying in degree from place to place, but all except the youngest children will have some experience of malaria and resistance to it

Amenability to control Very difficult to control Control by prevention of breeding would not be effective unless near-perfection is achieved, transmission continuing in the presence of very small residual breeding Control by imagicides would be relatively difficult, to be effective needing the achievement of a 40 or 50 per cent daily mortality among the vectors Control falling only slightly short of the necessary quality is not likely to produce much apparent result The "wearing out" of imagicidal control would be apparent at an early stage and would produce epidemics which would be severe but not necessarily abrupt in their timing

UNSTABLE MALARIA

Determining causes Transmission by a vector which bites man relatively infrequently If the vector were short-lived, or the temperature unfavourable to rapid completion of the extrinsic cycle, the characteristics of the type would be exaggerated These last two factors alone, without the rarity of feeding on man, would produce an intermediate type between this and stable malaria

Anopheline density needed to maintain transmission Relatively high, of the order of 1 to 10 or even more bites on each person each night

Endemicity Anophelism without malaria would probably occur in some localities, perhaps over considerable areas, as a result of breeding being insufficient to maintain the high densities needed for transmission In other places low to moderate endemicities would occur but would not necessarily predominate High endemicities might be common

Seasonal changes Likely to be very marked, in response to temperature changes, unfavourable breeding conditions or dryness of the atmosphere Seasonal epidemics would not be likely to occur till the temperature is relatively high, and would be likely to be brought quickly to an end by a drop in temperature Seasonal epidemics would be very abrupt and severe when they do occur, despite their late appearance

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Fluctuations in incidence Likely to be very marked, at times they would be due to causes so small as to be inapparent except

on close study They might take all forms, such as exaggerated seasonal epidemics, exacerbations of endemicity, or major regional epidemics, the first two tending to follow increase in breeding conditions, the last some climatic factor increasing longevity or breeding over a large area Equivalent reductions in local or general incidence could occur The invasion of previously non malarial areas by the disease and the reversion of malarious places to a non-malarious character are other aspects of the same fluctuation

Effect of cool weather Cool weather would rapidly bring this type of malaria to an end Mosquitoes biting man infrequen could not maintain malaria at high altitudes or latitudes Tran mission in summer–winter climates would be limited to the ho part of summer, starting late and ending early, but epidemics might be severe within this limited time

Immunity of the population As a result of the fluctuations in endemicity, and not as their cause, immunity would be very variable Circumstances could readily arise in which a notable part of the child population had a negligible experience of malaria in places commonly regarded as definitely malarious

Amenability to control Controlled with much more ease than stable malaria Moderate efficiency in prevention of breeding should be effective and control by imagicides is likely to be very easy, mortalities such as 20 to 25 per cent daily often being sufficient Control falling short of the desired degree would produce little apparent improvement, the "wearing out' of imagicidal control would not be apparent until a late stage but when this stage was reached would produce epidemics which would be both severe and abrupt in their timing

SPECIES OF PARASITE

An additional, though not essential, characteristic is that vivax malaria often predominates in unstable conditions, and falciparum malaria where they are stable The influence operating is the frequent interception of transmission in areas of instability, temporarily ending transmission before the more slowly multiplying *P falciparum* has established the predominance it would

otherwise attain, and which it in fact often secures in stable conditions This is not, however, invariable, transmission may be brief in some areas of stability, being limited by temperature or other ruling factor, and when this is the case *P vivax* gains the ascendancy, as for instance in many parts of southern Europe

HAPPENINGS IN NATURE

The full comparison of these two theoretically derived types with actual happenings in nature may be pursued on the two species which have already been named, *A gambiae* and *A culicifacies* The conformity in full detail is very close indeed

A gambiae appears to be highly anthropophilic, though it may be zoophilic in the extremes of its range The sporozoite rates commonly recorded in coastal equatorial Africa are only explicable on the basis of both a high anthropophilic index and a high longevity The normal mean temperature of that region is about 26° C, which probably permits the completion of the extrinsic cycle of *Plasmodium falciparum* in 12 days The critical density is certainly below 0 029 as Walton showed that this mean density permitted the continued transmission of malaria Anophelism without malaria has not been recorded Very high endemicities are extremely common, but are not invariable Seasonal changes other than temperature changes alter the amount of transmission, but rarely bring it to a complete end, entirely non-malarious seasons during the warm weather being very rare In those places where there is a winter the picture is complicated by cessation of breeding, but it seems that transmission starts soon after the advent of suitable temperatures Within the equatorial zone at low levels the stability of malaria carried by *A gambiae* is well known and acknowledged, marked changes from year to year being almost unknown Within this zone there is no recorded epidemic tendency The disease occurs at high altitudes, reaching 6 000 feet and sometimes greater heights Epidemics occur at these high altitudes and at the extremes of its distribution The epidemics at high altitudes are attributed mainly to variations in the probability of survival, and *A gambiae* may be zoophilic in these areas, the evidence is

not convincing, but if it were, it would give additional explanation of the epidemics The studies of Wilson which show the common acquisition of considerable resistance to infection are well known, and though the present writer disputes some deductions from it he does not dispute the essential fact The difficulty of control by prevention of breeding is well established Control by imagicides has had a variable degree of success

Malaria carried by *A culicifacies*, *A stephensi*, *A philippinensis* and *A superpictus* closely resembles the description of unstable malaria Although he has no personal experience of them the present writer thinks that the epidemiologies of malaria carried by the following anophelines also conform to this general description *A maculatus*, *A aconitus*, *A annularis*, *A punctulatus*, *A minimus* var *flavirostris*, *A albimanus* and *A aquasalis*

A culicifacies malaria will be given as a sole example The species is zoophilic but may feed predominantly on man when insufficient animal food is available Over long seasons of malaria transmission it is typically very short-lived, but when suitable climatic conditions, which are rather cool, occur it may be long lived The summer temperature over most of its range is hot enough to permit rapid completion of the extrinsic cycle The critical density is high, represented in Madras by catches of between 7–10 and 17–20 per man-hour, but it is probably considerably lower elsewhere, as there is evidence that the extremely low anthropophilic indices and longevity recorded in Madras are below the average Anophelism without malaria is well known In malarious localities high endemicities are quite common—a large part of Ceylon was hyperendemic until controlled—but low endemicities are also common The occurrence of seasonal variations in response to factors other than temperature change is very marked Different parts of Ceylon experience quite different seasons owing to differences in season of rain or humidity which are not themselves always marked, in fact the physical or climatic differences between neighbouring non malarious and highly malarious areas are often very difficult to discern Seasonal epidemics are typically very abrupt Fluctuations in incidence are extremely marked There are well known

epidemic areas in the Punjab and Ceylon, less well known ones in the Central Provinces of India and in Travancore, and Christophers and Sinton describe the epidemiology of malaria over a very large part of its range as being liable to fluctuations It does not occur at any considerable altitude, normally ending between 2,000 and 3 000 feet above sea level, but the validity of this as evidence is marred by the fact that this is near the upper limit of breeding The insecure immunity of the population in areas subject to this malaria has been described by Gill Personal experience shows that it is more amenable to control by prevention of breeding than malaria carried by either *A minimus* or *A gambiae* Control by imagicides has been brilliantly successful in a number of places, especially Ceylon

Malaria in the area infested by *A gambiae* is predominantly due to *P falciparum*, other species only contributing a small fraction of the total, whereas in areas infested by *A culicifacies* it is usual for *P vivax* to predominate This is consistent with the expected distribution of the two species in relation to the stability of malaria but the possibility of natural immunity playing a part offsets its value as evidence of cause and effect

There are not many species for which such a full comparison could be made but for several the general nature of biting habit, longevity, and associated epidemiological type of malaria are known and an estimate of longevity can be derived from the relation between oocyst and sporozoite rates In all cases examined it has seemed that there is an equivalent conformity between expected happenings and the actual In fact when classification of malaria is attempted in this way a great number of hitherto inexplicable and apparently unrelated epidemiological features of the disease are shown to be closely related, so that the picture of epidemiology falls into an orderly form This conformity is much too close and detailed to be explained on chance, and mathematical theory must be considered as confirmed by it So far as it relates to equilibrium it demonstrates the following key points which are most important in the epidemiology of malaria and of other insect borne diseases If the basic reproduction rate is below its critical value of 1 0, malaria will not remain continuously in the

population If it continuously exceeds this critical value, malaria will persist but its epidemiological characteristics will be largely determined by the biting habit and longevity of the mosquito When these together result in the average mosquito taking many blood meals on man in a normal lifetime, malaria will have the characteristics described as constituting stable malaria, and when they result in the average number of blood meals on man being very few, it will be unstable

MEASURES OF STABILITY

The types of malaria seen throughout the world range as a long series between the extremes of very high stability, as recognised in equatorial Africa, and the extremely unstable form occurring in northern India and in Ceylon A measure of stability has been used in South America, utilising the variation in the spleen rate the ratio of the maximum to the minimum rate observed in five years' time is described as the condition of malaria and indicates the degree of fluctuation observed In Venezuela, where the rate was described by Gabaldon, it varied between 7 and 1 In India the coefficient of variation of the fever mortality has been widely used as a similar index, figures in the Punjab varying from 31 to 106 These are direct measures of actual variation, but demand data for a number of consecutive years which may not always be available, and a measure indicating the probable stability of malaria, derived from more readily collected information, would be of value The most appropriate is an estimate of the number of bites on man taken by an average mosquito during a normal lifetime, which demands study of longevity, anthropophilism, and feeding habit The greater this value the more stable is the malaria conveyed likely to be The range in nature amongst known vectors probably varies from a maximum of about 10 down to 0 1 or even less It may be referred to as the stability index and the following classification can be used —

Stability Index		
Under 0 5	indicating	instability
0 5 to 2 5	,,	medium stability
Over 2 5	,,	stability

This classification is empirical, dividing up a continuous series, but it will be found that species which have a high anthropophilism and high probability of survival fall into the stable group, those in which one of these factors is low usually fall into the intermediate, and those in which both are low fall into the unstable group No exact classification of mosquitoes is possible, as for many of them our knowledge on these subjects is rudimentary, but a tentative classification of some notorious vectors is given to show relative positions in the scale

Vectors of unstable malaria

A culicifacies
A philippinensis
A maculatus
A minimus flavirostris
A stephensi
A messeae
A aquasalis

Vectors of malaria of medium stability

A atroparvus
A quadrimaculatus
A darlingi
A pharoensis
A hyrcanus sinensis

Vectors of stable malaria

A gambiae and *A melas*
A funestus
A minimus minimus
A fluviatilis
A sacharovi
A labranchiae

CYCLICAL CHANGES

Another aspect of equilibrium is a tendency to periodic change in the prevalence of malaria, apparently irrespective of changes in the controlling factors Recurring cycles with peaks at intervals varying from 5 to 20 years have been observed in many parts of the world, in Europe, the U S A , the Caribbean area, some parts of

South America, India and Ceylon, and are a very common feature of malaria, as of other diseases carried directly from man to man.

If a stimulus, such as infection, produces a restraining mechanism such as immunity, and the growth of the restraining mechanism is synchronous with the stimulus, a true equilibrium will be established with the two in balance. If the reaction does not occur simultaneously with the stimulus, true equilibrium cannot be established and some degree of periodic change is inevitable Stimulus and reaction are separated by a time which appears to be about two months in vivax malaria, and longer in falciparum malaria The stimulus, being temporarily unrestrained passes the degree at which equilibrium would be established if the reaction were simultaneous, and the immunity ultimately developed is commensurate with this excessive stimulus mo— than sufficient to restrain infection to the natural point (equilibrium In this way a seesaw motion is set up, infectio passing the median point, resistance depressing it below tha point, then dilution of resistance, and again exaggerated stimulus to its production In some degree this must happen in malaria of all types but mathematical analysis shows that the tendency is likely to be very much more marked in association with unstable malaria Once again this conforms to happenings in nature, the extreme cases of periodic movement occur where malaria is notoriously unstable and has the characters described in that connection they are best known in northern India and in Ceylon where the vector is *A culicifacies* Other examples come from places where equilibrium is moderately ur ... there are no known ones from places where it is stab ... there is no indication of its happening in the ... range associated *A gambiae* or in that of *A minimus*, w ... ma oscillation ... stable form of the the charac ... movement must ... unstable form

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CHAPTER V

EPIDEMICS

NATURE

AN epidemic is an acute exacerbation of disease out of proportion to the normal to which the community is subject There is a proposal to restrict the term to a narrower sense of outbreaks in places where the disease is rare, but the writer has found this restricted definition unworkable in practice and prefers the wider and more colloquial term Two main forms occur, the confusion of which may cause considerable difficulty, the epidemic due to simultaneous or recent transmission and that due to relapses of malaria transmitted some long time before The latter type is common in Europe and the northern temperate and subtropical zones, in which strains of *P vivax* show a marked tendency to latency either in incubation or between the original attack and the first relapse The result is the common occurrence of a spring epidemic starting in April or May, before transmission is established, and consisting entirely of vivax infections It reflects the amount of transmission in the previous autumn and provides the reservoir for transmission in the season which follows and though delayed it may be as debilitating to the individual and the community as any epidemic due to recent transmission The epidemic curve is usually of the bell-shaped form associated with random distribution round a mean, and the epidemic is normally near its end when the beginning of fresh transmission causes a fresh rise in cases The only means of handling such an epidemic is by treatment, and it is important that this should be undertaken in order to limit the reservoir from which new cases will later arise

The mechanism of an epidemic due to simultaneous transmission has been briefly described and is analysed mathematically in Appendix I It includes a series of phases in which the degree of multiplication of cases is progressively increased resulting in epidemic curves resembling those in Figures 5 and 6 when the

cause has an abrupt onset This is usually the case in epidemics precipitated by rainfall providing fresh breeding places, the emergence of the first new crop of anophelines often being roughly simultaneous In epidemics due to slowly operating causes, such as increase of humidity increasing anopheline longevity, the start is gradual and the step-like character is often blurred A part of Ceylon had the misfortune to supply epidemic data for many years, the typical form was visible in about half the cases, comprising those attributable to excess of breeding in the spring, and blurred in the other half following excess humidity in the autumn

Epidemics are common only in zones of unstable malaria, where very slight modification in any of the transmission factors may completely upset equilibrium, and where the restraining influence of immunity may be negligible or absent, and they therefore show a very marked geographical distribution Much of the history of South East Asia is recorded in terms of epidemics, whilst they are less common in the Mediterranean lands and the Americas and are virtually unknown in most parts of tropical Africa The exceptions to these statements demonstrate the general validity of the statement, epidemic malaria does occur in parts of tropical Africa, around the fringes of the main endemic area, both to its north and south, and at high altitudes where dryness or coolness shorten anopheline life or lengthen the period of the extrinsic cycle in relation to which it must always be considered

The apparent severity of an epidemic is a poor guide to the increase in transmission which has caused it Even small increases in transmission may in the end produce grossly disabling epidemics which seem dramatic to those who suffer them The distinction between those due to small and large causes lies very much more in the lapse of time between the first onset of the precipitating cause and the production of the epidemic peak, and even this may not differ very obviously unless the epidemic arises from a truly small origin It is usual for the initial phases, which may be prolonged, as is illustrated in Figure 8 (p 58), to be overlooked, after which the drama of one due to a four-fold increase in transmission may approach that of one due to a forty-fold increase

It is nevertheless of interest and value to try to decipher the scale of events which have precipitated epidemics in the past. In 1934–35 Ceylon suffered dramatic epidemics which attracted world-wide attention and which have been carefully documented by Briercliffe Construction of a synthetic curve which corresponded in form and scale with that actually occurring required the assumption that the reproduction rate had been increased to slightly over five times that ruling normally in the area, from 1 4 to 7 9, and that at the time when epidemic conditions began the parasite rate in the population was of the order of 5 per cent, a very probable figure in those circumstances Comparable though simpler examination of many natural epidemics suggests that most are due to increases of this order, or even less, which in unstable conditions is quite sufficient to precipitate an outbreak of dramatic severity

TYPES

Epidemics can be classed as long term, periodic, and irregular and these last may be further described according to their immediate cause *Long-term epidemics* may be so prolonged that it is hard to see them in perspective, though this does not affect their existence or importance Celli studied the history of malaria in Italy, showing four prolonged waves of incidence, separated by times of relative salubrity, since the beginning of the Christian era The picture throughout Europe has probably been much the same but only the decline of the last epidemic, from 1750 to the present time, is well known During this time malaria has receded from a position of very general distribution and wide importance to a few limited foci and now perhaps to extinction Recession was interrupted by many recrudescences and epidemics Some of them showed a periodic tendency with a cycle of about 20 years and some occurred irregularly and often in association with wars or other domestic distress, characteristics which have persisted up to the last war in the remaining foci of infection The North American continent has been the scene of a great epidemic which started early in the seventeenth century, reached its peak about 1870, and then progressively declined until it was abruptly terminated by the U S A Malaria Eradication Programme which

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began in 1947 A briefer wave started in the Malay Peninsula in the last years of the nineteenth century, causing great suffering The severity of the epidemic was maintained up to 1932, when progressive decline started It was interrupted on a number of occasions and notably at the start of the Japanese occupation in 1942 since when however, it has decreased steadily The causes of these long waves cannot be certainly determined and must largely remain the subject of inspired guesswork It is certain that they were on the whole small, representing minor increases and decreases in the facility of transmission, which explains the difficulty in discerning them accurately Decline has been commonly associated with improvement in the social and economic welfare of the people but the exact aspect of that improvement which has produced the result is not known Anyone with too ready an answer might consult the highly analytical study by Brumpt which demonstrates the invalidity of most accepted theories in one place or another Probably the major influence in causing a decline has been a change in agricultural pattern which has resulted in some deviation of anophelines from man to cattle, but the influence of changing population pattern with a smaller reservoir of non immune infants in countries with a low birth rate, and that of migration in upsetting the balance of immunity, are not to be ignored

Cyclical changes in the endemicity of malaria producing *periodic epidemics*, and less well noted periodic times of relative freedom are very well known and probably occur in some degree in most parts of the world affected by unstable malaria An explanation for them has already been put forward in Chapter III They have been documented in the U S A , the Caribbean region, in much of South America and especially the Argentine, in Ceylon and in India The degree of cyclical change varies considerably The places where it is great have become notorious epidemic centres happenings in which have given rise to descriptions of a special type of epidemic known as fulminant, the best known being in India and Ceylon The main Indian centre is in the Punjab where disabling epidemics have occurred as far as can be traced back in history at intervals of about 8 years That of

in the seventeenth century, and most other recorded examples are probably cases of re-introduction into places whence the disease had previously disappeared There have been many recent examples connected with the movement of people in war, and in some it has been possible to trace events from the start In the recent re-introduction into Grand Canary Island the primary case, the immediate secondaries, and the subsequent spread could all be traced There was an initial highly localised but very fast burst of transmission, followed by a more sedate expansion over a wide area, and that in turn by an equally sedate disappearance and elimination Disappearance was aided in this case, but the history of northern Europe shows that introduction, spread and subsequent elimination may well follow each other naturally This form of re-introduction has probably always happened in places where the reproduction rate was naturally low, and so low that at some time in the past a small degree of communal immunity had been enough to reduce it below the critical level and cause elimination of the disease Re-introduction has been possible because this reinforcing immunity disappeared with freedom from malaria, but a few years of exposure have stimulated it again ir sufficient degree In the future, however, re-introduction may occur into places whence elimination has been by deliberate control, and where the natural reproduction rate, unrestricted by immunity or continued control, might be very high In consequence the history of past examples may be a poor guide to the future, from which some extrapolation from known happenings on the basis of theory, such as is presented later in this chapter, is needed

Most records of the fresh introduction of potent vector anophelines concern the migration of *A gambiae* It is thought to have reached Mauritius some time shortly before 1865 Sporadic cases and small outbreaks occurred in that year, they were followed by severe epidemics over a small area in the next, and by wide and devastating epidemics during the following season when a quarter of the inhabitants of Port Louis died, and the general death rate for the island rose to 120 per 1,000 During this third season it conquered the island, which remained severely affected until

recent control schemes brought malaria to a virtual end The neighbouring island of Reunion was affected similarly shortly afterwards Comparable severe outbreaks of malaria occurred in 1906–7 in Durban, which had previously been free from the disease, and they were probably due to a similar invasion These recorded examples probably represent a general happening during the last century in many parts of the present southern range of *A gambiae* The same mosquito, normally limited to Africa, was found in Natal, Brazil, in 1931 having migrated by ship Localised epidemics of extreme severity happened at the time of its first discovery, after which there was a steady extension of its range until in 1938 it had infested a strip of coastland some 5,000 square miles in extent In that year devastating epidemics accompanied by very high death rates occurred throughout the infested area and led to the fear that *A gambiae* might become disseminated throughout South America and reduce it to the malarial state of Africa This emergency was met by a successful *gambiae* eradication scheme based on larvicidal practice, using Paris green and the administrative techniques developed in the eradication of *Aëdes aegypti*, and ended in the destruction of all members of the species, thereby setting a pattern used in later anopheline eradication schemes These happenings were almost repeated when in 1942 severe epidemics of malaria in Upper Egypt from the Sudanese frontier to Assiut drew attention to the wide prevalence of *A gambiae* which had not previously been recorded from this area and must clearly have migrated from the south The deduction was made that invasion had occurred at that time but the history of the rate of extension in Brazil and other places makes it more probable that the first introduction had occurred some considerable time before The emergency was met by an eradication scheme closely resembling that carried out in Brazil, and with equally successful results

These migrations have been made dramatic by the extreme potency of *A gambiae* as a vector and have been facilitated by its catholic choice of breeding places, but they probably only represent the more recent and dramatic examples of many migrations, most of which can only be seen dimly in the past It is for instance

highly likely that *A sacharovi* has made comparable migrations Certainly one of the most malarious foci in the Levant, the neighbourhood of Lake Huleh where it is the vector, was regarded by the Romans and by crusading armies in the Middle Ages as a health resort for some centuries before it suddenly became insalubrious The principal risk of future happenings lies in Australasia and the Pacific, and in the possible migration of *A punctulatus punctulatus* into lands apparently suitable for it but now free from important vectors

Abnormal increases in anopheline density producing epidemics may be due to natural factors causing a *multiplication* of breeding places of the vector species, and at times to factors which would not at first thought be suspected In Ceylon the stage is set by drought, and it is only the final raising of the curtain that can be attributed to light rainfall replenishing the pools in dried up river beds which are favoured as breeding places by the local vector, *A culicifacies* Most commonly however the abnormal multiplication of mosquitoes is due to human activity, and the resultant epidemics are properly described as man-made malaria As with all causes the effects are in proportion to the instability of the disease and the risk is much greater in some lands than in others South East Asia has suffered particularly, and much from the construction engineer whose borrow-pits and obstructions to natural drainage by roads, railways and ill-laid culverts have provided innumerable breeding places for *A culicifacies* and other carriers The health of the entire State of Bengal, for instance, deteriorated during the last century largely owing to this cause. Other activities and other people have, however, produced comparable results The indiscriminate clearing of jungle, and consequent exposure of streams to the sun, by planters in India and Malaya led to the multiplication of *A fluviatilis*, *A minimus* and *A maculatus* until the relation between cause and effect in the shape of epidemic malaria was recognised In the Americas the impounding of water has provided lakeside breeding places of *A quadrimaculatus* and the construction of irrigation systems made ideal sites in which *A darlingi* proliferated, to the extreme disadvantage of neighbouring people Such examples could be

multiplied indefinitely, they have led to wide condemnation of the activity of the engineer, who has often retaliated with comment on the uncooperative attitude of the malariologist and medical man To some extent the engineer is right, development means engineering which should be directed in this respect and not obstructed One of the most helpful mechanisms for direction has been the institution of systematic courses in the epidemiology of malaria for engineers, which are now very commonly attended in India and are becoming appreciated elsewhere

Increase of the man-biting habit by deviation of anophelines from animals to man may occur in the countryside following deprivation of cattle, or in towns where they are not normally present in numbers In the countryside deprivation has often been due to war, exacerbation of malaria in Okinawa following the last war and due to this cause is well documented, there have been many outbreaks in Europe during both the great wars of this century, attributable to normally zoophilic members of the maculipennis group such as *A messeae* turning perforcedly to man for food Such deviation is probably a major element in the malaria of labour forces, which in their early stages do not typically own cattle though they may create breeding places One of the precipitating causes of Punjab epidemics is economic hardship amongst the people and it has been reasonably postulated that the mechanism is through reduction in the numbers of cattle The spread of zoophilic species into town areas has a like effect, which has been documented in connection with the spread of *A culicifacies* in Delhi, and *A hyrcanus sinensis* in Indo-China, in each case with a demonstration of the enhanced anthropophilism which led to severe outbreaks *A stephensi* is usually highly zoophilic, and in the countryside of Bombay State conveys a very unstable malaria or none at all, but within the city it can find breeding places and even a small prevalence causes severe endemic malaria

Interest in the relation between changing longevity and epidemics was first aroused in the Punjab where it was shown by Gill that floods precipitated epidemics though they did not cause a multiplication of breeding places for the local carrier Their influence

be cut short by climatic changes before it has reached its peak In such places unusual prolongation of the transmission season by climatic variations leads to epidemics, which are well known in Morocco in years when warm weather is prolonged unusually into the autumn

EPIDEMICS DURING OR AFTER ERADICATION OF MALARIA

There is little experience of this form of epidemic but it may well become the most common or almost the only type Any recrudescence during an eradication programme would be an epidemic, and a main object of workers in such a programme would be to discover the epidemic whilst it was still of what would in other circumstances be called negligible size The type therefore deserves some considerable analysis in an effort to foresee the order of events which might be expected and to plan to recognize examples.

Such epidemics would differ from most others in the past in that they would arise from very small origins, perhaps from one or two individuals in a community, and might occur in areas previously subject to either stable or unstable malaria In principle they would resemble any others but there might well be considerable differences in degree The original source would probably be a chronic case, either a late vivax relapse or an old falciparum infection, perhaps in an immigrant The source is likely to be in a person with some immunity which would protect him from clinical effects and might well therefore lead to his escaping detection This immunity would probably also make the original case relatively poorly infective, with a low density of gametocytaemia resulting in the infection of only a small proportion of the anophelines feeding on it, and in only low grade infections in most of the mosquitoes infected, resulting in their poor infectivity to man The numbers of secondaries arising directly from this source is therefore likely to be relatively small These secondaries, though not numerous, would probably be non-immune and display the characteristics of a fresh infection, notably the prevalence of large numbers of highly infective gametocytes in

the blood for a considerable period of time. The true growth of an epidemic through the population may be considered as arising from them.

Happenings from this starting point would follow the principles described in Chapter III, through a series of phases representative of the incubation interval, in the first of which there is no increase, in the second an arithmetical increase, and in the third and subsequent ones a geometrical increase in the daily increment of new cases, the ratio of increase growing greater in each interval. The length of the incubation interval and the nature of the reproduction rate determine the scale of multiplication. The mathematical background, which is set out in Appendix I, is complicated. A large number of synthetic curves have however been worked out in full, and in the process it has been observed that, until the incidence becomes high, progression is very regular and nearly of a simple multiplicative type. In dealing with the small origins of epidemics rather than with the detail of their peaks it is reasonable to make a simplification expressing the approximate course of events and this is here presented in an empirical statement, the justification for which is given in the mathematical section.

Happenings may first be considered for an incubation interval of 20 days, which is taken as generally applicable for vivax malaria. Infective cases occur at zero time. For the period of one incubation interval there would be no secondaries. In the second interval they would occur, and in such numbers that at the end of it the proportion of the population affected would be represented by:

$$x_2 = x_1(0{\cdot}22z + 0{\cdot}8)$$

where x_2 is the proportion affected at the end of the period
x_1 is the proportion originally (the primary cases)
and z is the reproduction rate.

In successive intervals after this the proportion affected would be multiplied in a very similar manner, except that the value of the factor by which z, the reproduction rate, is to be multiplied varies with the value of that rate in roughly the following form:—

Reproduction rate	*Multiplying factor*
1– 3	0 20
4– 7	0 18
8–17	0 16
18–49	0 14
50 and over	0 12

Thus if the reproduction rate were 50, and the original cases amounted to one in a thousand of the population or 0 001, the parasite rate might rise in one interval to 0 001 × 11 8 or 0 0118 In the subsequent interval this would be multiplied by 6 8 to 0 08, and again in the next to about 0 55 or 55 per cent The epidemic would then be at its peak some 80 days after the occurrence of primary cases and 60 days after the appearance of secondary cases derived from them For a reproduction rate of 20 the course of events would be roughly as follows at the end of the first interval 0 001, at the end of the second 0 0052, this value being multiplied by 3 6 (i e 2 8 + 0 8) in each subsequent interval to give parasite rates of about 0 019, 0 067, 0 243 and 0 84 at the end of each In this case the apex of the epidemic would be reached near the end of the sixth interval, 112 days from the occurrence of the primaries and 92 days after the first appearance of secondaries In this series the successive generations of secondary cases represent 0 4 per cent, 1 4 per cent., 4 9 per cent, 17 5 per cent, and 63 1 per cent of new cases in the population It is clear that the last would constitute a locally calamitous epidemic of great severity, the fact that it arose from a low reproduction rate being revealed much more by the relatively prolonged period of genesis than by any mildness in the epidemic which would ultimately result It would *clearly be the function of a surveillance service to detect such an* outbreak in the period of genesis, and certainly within the first two generations of secondary cases

Comparable synthetic figures can be calculated for any value of the reproduction rate, but to save laborious tables of figures a number have been constructed as epidemic curves in Figure 8 These represent the total cases or parasite rate; the proportion of new cases in any interval is calculable by comparison of the

of epidemics due to it, occurring when roughly 50 per cent. of the population is infected, must inevitably be later than that due to vivax malaria, even when transmission is intense. There is in both cases a phase of relatively slow growth, representative of the initial broken step often seen in epidemic curves, but this may be followed by a sudden transition to a dramatic rise. When the origins are small as here postulated this only occurs at once if the reproduction rate is high, but it can also occur when epidemics due to lower rates spring from larger origins. The initial relatively slow stage is a warning of what is to come and towards its end it is a warning of what is already incubating in man and mosquito. If secondary cases are recognised there should clearly be an urgent study of their numbers and the period for which they have been prevalent, which will dictate the urgency with which emergency insecticidal and perhaps mass therapeutic measures should be undertaken. Therapeutic measures may be urgently indicated if it is feared that any notable proportion of the people are incubating falciparum malaria, though if vivax malaria only is to be feared it may be preferable to permit the demonstration of actual cases at the time when special treatment facilities can be given, rather than prolong the incubation period for months by abortive prophylaxis and cause a later outbreak of relapses after the sense of urgency had passed.

In many countries transmission is limited by season, the epidemic curves here illustrated being cut short after a varying period, often of about 150 days in the malarious Mediterranean zone, when the importance of recrudescence would turn largely on the severity of transmission and on the time of its commencement. The past history of much of the Mediterranean lands suggests that normally there has been ample time for the full development of vivax epidemics within the season. They have, however, usually arisen from greater origins than here postulated, and those from really small origins might well be cut off before reaching their summit. Past records of the summer parasite rate amongst young children, and especially of the relative prevalence of vivax and falciparum malaria will throw some light on this, though it is to be remembered that past happenings have

largely been tempered by communal immunity restricting the reservoir of infection and thus the speed of development of epidemics

CONTROL

There are only two radical means of dealing with epidemics; one is to recognise them in their very early stages, before any notable part of the population is affected and to prevent their further spread, the other is to stop them with drugs Any measure of mosquito control must be secondary to drug treatment or prophylaxis once an epidemic is established if needless suffering is to be avoided Even immediate imagicidal control leaves many incubating the disease, and larvicidal control cannot be expected to influence the epidemic for at least a month and perhaps longer The most valuable drugs are those which can cure in the smallest possible number of doses, and which combine curative and preventive properties For most circumstances the 4-amino-quinolines are the most appropriate, chloroquine or amodiaquine in a single dose of 0 6 G of the base immediately to sufferers, and in weekly doses of 0 3 and 0 4 G respectively to others, with appropriate modifications for people of different ages Mepacrine has proven too toxic for use in such conditions, unusual numbers of cases of ill-effect being perhaps connected with malnourishment often associated with the epidemic disease Pyrimethamine in doses of 25 mg, and proguanil in doses of 0 3 G, have not the same general applicability as their curative value against some strains of malaria may be low, but in some places they may be equally useful and in others they are likely to be of some value if the 4-amino-quinolines are not available An immediate ending to dramatic happenings can be expected to follow, but radical cure of vivax infections will not follow such treatment and other mechanisms to make fuller treatment available will usually be needed

The mathematical theory here described is elaborated in —

MACDONALD, G The analysis of malaria epidemics 1953, *Trop Dis Bull*, 50, 871–889

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The mathematical theory here described is elaborated in —

MACDONALD, G The analysis of malaria epidemics 1953, *Trop Dis Bull*, 50 871–889

MACDONALD, G Theory of the eradication of malaria 1956, *Bull Wld Hlth Org*, 15, 369–387

ARMITAGE, P A note on the epidemiology of malaria 1953, *Trop Dis Bull*, 50, 890–892

Long term epidemics can be studied in —

BOYD, M F An historical sketch of the prevalence of malaria in North America 1941, *Amer J trop Med*, 21, 223–244

CELLI, A *The history of malaria in the Roman Campagna from ancient times* Edited and enlarged by Anna Celli-Fraentzel London John Bale, Sons and Danielsson, 1933

The scientific study of the epidemic originates in —

CHRISTOPHERS, S R *Malaria in the Punjab* Scientific Memoirs by Officers of the Medical and Sanitary Department of the Government of India New Series No 46, 1911

which is, however, hard to obtain

There are general studies in —

CHRISTOPHERS, S R *Endemic and epidemic prevalence* Chapter 27 in M F Boyd's *Malariology* Philadelphia and London W B Saunders Co, 1949

GILL, C A *The seasonal periodicity of malaria and the mechanism of the epidemic wave* London J & A Churchill, 1938

and excellent detailed studies of individual epidemics in —

BRIERCLIFFE, R *The Ceylon malaria epidemics* 1934–5 Ceylon Sessional Paper XII Colombo, 1935

COVELL, G & BAILY, J D The study of a regional epidemic of malaria in Northern Sind 1932, *Rec Malar Surv India*, 3 279–322

GARCIA SASTRE, L Notas sobre el paludismo en la isla de Gran Canaria 1945, *Rev Sanid Hig publ (Madr)*, 19, 257–271

RAJENDRAM S & JAYEWICKREME, S H Malaria in Ceylon. Pt I The control and prevention of epidemic malaria by residual spraying of houses with DDT 1951, *Indian J Malar*, 5, 1–73

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CHAPTER VI

LOCAL FEATURES OF MALARIA

(1) GENERAL CONSIDERATIONS

GENERAL DISTRIBUTION

IALARIA is not transmitted except at temperatures exceeding 5° C, and this temperature must be maintained for a month or nore for it to become established even when potent vectors are resent The less potent ones do not usually maintain transmission nless a somewhat higher temperature is kept up for a longer time n consequence the extreme limits of malaria in the northern emisphere lie within the July 15° C isotherm and are almost dentical with it In the south they do not reach this isotherm, argely owing to the absence of potent vectors in the areas pproaching it Within the extreme limits there are many non-nalarious zones, some free because they are arid and provide ieither breeding places nor environment appropriate for trans-nission, and others because they have not been invaded by ano-heltnes which are fully adapted to transmission The first include lesert zones such as the Sahara and the second a large part of the 'acific archipelago including most islands east of Australia except he Solomons and the New Hebrides Altitude limits distribution n a variable way as it influences breeding conditions and in a more egular way as it is associated with temperature variations Where potent vectors are present the disease occurs at considerable ieights in the tropics at 7,000 feet in Kenya where it is carried by *A gambiae* and *A funestus*, at 6,000 feet within the zone of *A minimus* in the Indo Chinese hills and at 7,000 feet within he Andean distribution of *A pseudopunctipennis* Elsewhere the disease usually comes to an end at lesser heights, varying with atitude and hence with the temperature at different heights, the occurrence of the types of breeding place which are appropriate o the vector and their occurrence in mountains, and with the potency of the vector A mosquito which, owing to its typically

short life or zoophilic habit is a poor vector, will cease to be effective in maintaining transmission following a lesser reduction of temperature, and therefore at lower altitudes, than a well adapted vector Thus, in the Lebanon *A sacharovi* carried the disease (until the era of control) at a greater height—3,000 feet—than *A superpictus* which could not keep up transmission above 2,000 feet, though at sea level they were both important carriers

ANOPHELISM WITHOUT MALARIA

Within the limits of malarial transmission there are many places infected by an apparently appropriate vector, which enjoy a suitable temperature and other environmental conditions, in which malaria does not prevail and from which it tends to die out if introduced The state is known as anophelism without malaria and has attracted much attention It is widespread in Europe, and was inexplicable until the demonstration that the *maculipennis* group of mosquitoes was not homogeneous but included many mosquitoes of different characteristics appeared to supply an answer, in that the distribution of malaria roughly followed that of the more potent vectors The explanation proved in the end to be only partial, *A atroparvus* is an efficient vector member of the group but, as was pointed out by Hackett, there are numerous areas of atroparvism without malaria, and in fact the disease only occurs within a very small part of that mosquito's range Some of the other members, such as *A messeae*, are in some circumstances carriers, and the rest of the areas they infest must be looked on as areas of anophelism without malaria Such healthy places are well known in India Russell and his co-workers studied large malaria free parts of Madras and established the fact that the mosquito which infested them, *A culicifacies*, was in fact the same species as that which infested neighbouring malarious zones and as susceptible a carrier There are enormous tracts of healthy land within the range of *A quadrimaculatus* in North America, many within the distribution of *A aquasalis* and *A albimanus* in Central America *A hispaniola* carries the disease within only a very limited part of its range in North Africa, *A superpictus* carries in the warmer parts only of the Mediterranean region, *A punctulatus*

farauti has caused wide outbreaks in Australia but is not normally associated with transmission

These examples could be repeated round much of the world, but repetition would come to an end once examples were looked for in others Anophelism without malaria does not happen in the range of *A sacharovi* or *A labranchiae*, and is unknown within that of *A gambiae* or of *A minimus* It is a phenomenon associated with instability of malaria and occurs where the vector is short-lived, or is zoophilic, or where cool temperature extends the extrinsic cycle of the parasite to make the anopheline short-lived in comparison with it It is demonstrable evidence of the critical density of mosquitoes, the areas free from malaria are those in which prevailing conditions do not bring the reproduction rate above the critical level, indeed, Russell was able to demonstrate a critical level in the Madras examples which have been quoted Within the range of zoophilic or short-lived mosquitoes—and those in Russell s case were both—the critical density is high and such that breeding often occurs without being sufficient to bring the density above it For *A gambiae* in most of its range the critical density is very low, experiment has shown that it is under one mosquito to 30 people in one place, and such that if breeding is occurring the density is almost invariably exceeded though there is a theoretical minimal level it is not observed in nature

The condition represents a potential risk in that qualitative changes in the area may readily lead to the critical density being passed and transmission being established, and such has often happened Epidemics which are very difficult to explain may arise as a result, often they temporarily establish an endemicity which may, however, diminish as imperceptibly and unaccountably as it arose Some material change in the locality may lead to the long establishment of malaria which may be very severe Faults in the Cauvery Canal irrigation project led, for instance, to the establishment of severe malaria in large parts of Madras which had previously experienced anophelism without malaria, but in most of these places the disease died down 10 to 20 years later, quite inexplicably except on the basis that a communal immunity

had by then been built up which was sufficient to bring the reproduction rate down below its critical level again

REGIONAL DISTRIBUTION

The map presented in the endpapers shows twelve malarious regions and one non-malarious area bordering them The map has been drawn with an awareness of the zoo geographical regions of the world, within which animal species including anophelines tend to be limited There has, however, been no detailed following of those regions, but rather an attempt to define areas in which the epidemiology of malaria is of the same nature throughout and this turns on temperature, rainfall, seasons, physical features of the land and other factors as well as on the distribution of anopheline species The zones shown are epidemiologically distinct and happenings in one may be in marked contrast with those in its neighbours though there is a certain homogeneity within each of them The sections which follow give an outline of happenings in each, but the student who may have a particular concern with one of them is recommended to elaborate his reading considerably for which he may find some of the literature quoted at the end of the sections helpful

Anophelism without malaria is described in —

BRUMPT, E Anophelisme sans paludisme et regression spontanee du paludisme 1944–5, *Ann Parasit hum comp* 20 67–91

HACKETT, L W *Malaria in Europe* London Oxford University Press 1937

RUSSELL, P F & RAO T R A study of the density of *Anopheles culicifacies* in relation to malaria endemicity 1942, *Amer J trop Med*, 22, 535–558

JAMES, S P The disappearance of malaria from England 1929 *Proc roy Soc Med*, 23 71–85

high altitude malaria is described in —

GARNHAM, P C C The incidence of malaria at high altitudes 1948 *J nat Malar Soc*, 7, 275–284

HACKETT, L W The malaria of the Andean Region of South America 1945, *Rev Inst Salubr Enferm trop (Mex)*, 6 239–252

and the general distribution is well documented in —

HACKETT, L W Distribution of malaria Chapter 28, pp 722 735 in M F. Boyd s *Malariology* Philadelphia and London W. B Saunders Co , 1949

(2) THE AMERICAS

In the three zones indicated in the Americas the epidemiology of malaria is fortunately now becoming largely a matter of historical and academic rather than practical interest, because campaigns carried out since 1945 have eliminated much of it and the decision of the Pan-American Sanitary Bureau in 1955 to co-ordinate efforts at total eradication may well soon result in the disappearance of most of the rest The history of the northern zone has been outlined, invasion early in the seventeenth century was followed by spread to the limits indicated in 1870, since when there has been a steady decline In 1947 malaria affected some of the southern parts of the U S A but an eradication campaign started in that year has since ended it The chief carrier was *A quadrimaculatus*, a zoophilic mosquito which turns to man in the absence of its preferred hosts, and maintains an endemicity of intermediate stability *A freeborni* had at one time also been a carrier of very unstable malaria in the western states but only where conditions were made peculiarly favourable for it to do so, especially by the development of extensive rice cultivation unassociated with animal farming Both these mosquitoes are members of the maculipennis group, and favour the peripheral vegetation areas of impounded waters and swamps as breeding places, malaria tending to be associated with such water types The disease was seasonal, occurring as summer waves which were prolonged in the south It was much exacerbated by water development *P vivax* predominated throughout most of the zone but *P falciparum* was plentiful in the southern states The control scheme operated by the Tennessee Valley Authority on a series of great lakes which it had created became very widely known for its extent, the integration of engineering and health measures, and the originality of some of the methods used In common with all others it was superseded by the national campaign of 1947 which

aimed at eradication of the disease. Control was concentrated in those states where mortality figures indicated a material prevalence, it started with a general attack by means of residual insecticides in affected districts, which was discontinued when endemicity reached negligible levels, and replaced by an individual case-searching and treatment mechanism. Successive areas have been declared free and only one notable recrudescence has occurred despite the importation of many thousands of infected soldiers who have suffered from relapses of vivax malaria contracted in Korea.

The central American zone is tropical, and temperature would permit transmission in most parts of it throughout much of the year. The principal vector is *A. albimanus*, essentially a non-domestic species which infrequently enters houses, though when it does so it bites man readily. Precipitin tests have shown as many as 34 per cent. to have taken human blood but this may reflect the place of capture more than the general source of food. Recorded sporozoite rates are all low, usually below 0·6 per cent. It breeds by preference in sunlit pools and has a wide distribution throughout central America, in the Caribbean, and in the north-western coastal areas of South America. It is aided as a vector by other species: by *A. aquasalis* in many coastal areas and by *A. punctimacula* in Panama and perhaps elsewhere; *A. darlingi* is a vector in parts of the isthmus, and *A. aztecus* maintains a low endemicity of vivax malaria at considerable heights—up to 6,000 feet or more—in parts of Mexico.

Malaria is generally *moderate in incidence, rarely* aching the
hyperendemic levels common in Africa, and derately
unstable in type. Epidemics, the *alternatio* y and
unhealthy years, cycles of incidence and a tho
malaria are all kno d, as is characteristic mu
harm has been emics of the dis
variations in i *place to place*
prevalence of b , as is also usu
picture. In most *vivax* predomi
is secondary to it, is rare, but t
examples of islan from *P. vi*

past has been largely by anti-larval means and has not on the whole assumed great urgency except in special areas such as around the Panama Canal Mexico has now, however, embarked on a national scheme for the eradication of malaria with the aid of WHO and UNICEF, the principle has been generally accepted and there are programmes of control in most of the islands, which may be expected to extend to all of them during the next few years

In South America the main carrier is *A. darlingi*, which is widely distributed in Brazil and the parts north of it, though not on the western coast It has been reasonably postulated that its natural home lies in central Brazil, where it feeds on both man and animals and rests both in houses and outdoors, but that extension from this centre has been by specifically anthropophilic strains following man until the mosquito attained its present spread Away from the centre *A darlingi* is very firmly anthropophilic and closely associated with man, resting almost invariably in his houses and shelters and feeding almost exclusively upon him Despite this the malaria carried is never as severe as that seen in Africa and is only moderately stable, fluctuations and epidemics being common, while sporozoite rates are generally low It seems probable, but it is not confirmed, that the mosquito is generally short-lived It is mainly a lowland species, prospering in the plains, breeding in swamps irrigation channels and in the neighbourhood of tall vegetation, but sometimes in the grassy edges of rivers and occasionally even in stony rivers Choice of breeding place is partly determined by the reaction of the water and there are rivers in the northern coastal area in which the water is of high pH and which are unsuitable for it They are identifiable because the water is often black and their unsuitability has been utilised in establishing quarantine zones to prevent re-invasion of areas freed from it Other vectors include *A albimanus*, which has been mentioned in describing the central American zone, which is present in the coastal belt of the north and east, *A aquasalis*, *A pseudopunctipennis* and members of the *Kerteszia* group *A bellator* and *A cruzi* *A aquasalis* breeds in saline water and is confined to coastal districts except for occasional foci in inland places where waters are saline Within the coastal zone its larvae are found in swamps,

streams, and even minor depressions and often in thick vegetation It is highly zoophilic, evidence suggests that normally it is very short-lived and may suffer a daily mortality of 30 per cent or more, it bites out of doors and is not associated closely with man On all counts it should be an extremely poor vector, and in fact it only gains importance by the vast numbers in which it may occur near favourable breeding sites, and even so this importance is strongly influenced by the availability of animal food Sporozoite rates are invariably extremely low, even below 0 01 per cent, and many surveys have ended without the recognition of an infective mosquito The nature of the breeding place, the need for very large numbers to keep transmission up, and the common avoidance of houses, all tend to make control by drainage preferred to imagicidal techniques Often, however, control may be unnecessary as this species may sometimes only perpetuate a transmission established by another species

A pseudopunctipennis is the vector of the Andean slopes and the west coast, from northern Chile to Venezuela, and in the Andean area it may maintain transmission up to heights of over 7,000 feet It has been suggested that it represents a complex of species or strains because its habits vary greatly from place to place In the southern and Andean parts of its distribution it is anthropophilic and a potent carrier, in Venezuela it is zoophilic and a poor one, while in the islands it is looked on as unimportant Its influence is limited by its demands of breeding places, largely pools in the beds of rivers and streams from which it is displaced by flood so that breeding is favoured by dry weather

Two members of the *Kerteszia* group, *A bellator* and *A cruzi* are important vectors, and one—*A homunculus*—may be They are characterised primarily by their choice of breeding place in water resting in bromeliad plants, epiphytes living on the branches or trunks of trees and independent of the soil Mosquitoes of the group bite out of doors and in broad daylight, and are effective vectors of malaria By these characteristics they present a problem which is quite different from any malaria problem elsewhere in the world The bromeliad is dependent on the maintenance of a water reservoir for its metabolism and is confined to wet and

humid districts where it becomes established on trees of certain species, with the result that bromeliad malaria is a disease of coastal areas in Trinidad and Brazil, its local distribution being determined by the nature of climate and of vegetation To a considerable extent it is an occupational disease, affecting workers on plantations, and it presents special problems of control which may be by the destruction of bromeliads or of the trees on which they find support

Full general descriptive accounts, with much documentation, are to be found in —

FAUST, E C Malaria incidence in North America Chapter 30, pp 749–763, in M F Boyd s *Malariology* Philadelphia and London W B Saunders Co, 1949

GABALDON, A Malaria incidence in the West Indies and South America Chapter 31, pp 764–787, in M F Boyd's *Malariology* Philadelphia and London W B Saunders Co, 1949

Accounts of aspects which are of special interest are to be seen in —

BOYD M F An historical sketch of the prevalence of malaria in North America 1941, *Amer J trop Med*, 21, 223–244

DOWNS, W G & PITTENDRIGH, C S Malaria transmitted by bromeliad-breeding anophelines Chapter 29 in M F Boyd s *Malariology* Philadelphia and London W B Saunders Co, 1949

KUYP, F VAN DER *Contribution to the study of the malarial epidemiology in Surinam* Koninklijke Vereeniging Indisch Instituut, Mededeling No LXXXIX, Afdeling Tropische Hygiene No 18 1950

and especially interesting accounts of control in —

GABALDON, A. The nation wide campaign against malaria in Venezuela 1949 *Trans roy Soc trop Med Hyg*, 43 113–160

RUSSELL, P F, ANDREWS, J M, GABALDON, A, GIGLIOLI, G, PINOTTI, M & SOPER, F L Symposium Nation wide malaria eradication projects in the Americas 1951, *J nat Malar Soc*, 10, No 2

(3) EUROPE AND NORTHERN ASIA

NORTH EUROPEAN AND ASIATIC ZONE

The primary characteristic of this zone is that a long cold winter prevents transmission for at least half of the year and that for part of the remainder the temperature is below the optimal It lies

within the palaearctic region but is separated from an important part of it described later as the Mediterranean zone because the epidemiology of malaria is greatly different in the two parts

The normal brevity of the season and the coolness of much of it deters the multiplication of *P falciparum* which is rare in most parts of the area except southern China, *P vivax* being everywhere predominant and in many places the only parasite present. Malaria has been widely distributed within the area It has disappeared from most of Europe in a spontaneous recession covering a couple of centuries, to which reference has already been made, but the continued susceptibility of the area to endemicity has been demonstrated by many local outbreaks during the last two great wars Apart from these outbreaks, which have been widespread in central and eastern Europe and in Spain, the last remaining foci have been in the Danube Basin, in Holland, Portugal and Spain

The potential vectors which are present are not especially attracted to man, with the possible exception of *A sacharovi* which is said to be present in parts of China The commonest carrier is *A atroparvus*, which is long lived and feeds readily on man if no other source of food is easily available It can therefore become a potent carrier though it may not be one when numerous cattle are available as a source of food It breeds most readily in slightly saline water and is in consequence on the whole a coastal species, prevalent around estuarine marshes and in areas liable to tidal inundation, from which it is being slowly expelled by land reclamation *A messeae* is a capable vector, and is widespread because it has no preference for salinity in its breeding places, but is much less ready to turn to man as a source of food There have been many outbreaks of malaria attributable to it, perhaps much of the old endemicity was maintained by it, but recent transmission has only been in areas where breeding was profuse and cattle were absent

The extent of penetration of these species to the east is not properly known In the far east, in China, *A sacharovi* is reported as present, but *A pattoni* is probably the main carrier in the northern parts and *A hyrcanus sinensis* in the southern parts

included within this area Both are swamp breeding species and primarily zoophilic, but turn to man when need be and then transmit malaria of an intermediate stability

THE MEDITERRANEAN ZONE

This zone includes Europe south of the Alps, and also the Levant to and slightly beyond the Caspian Sea The summer climate is hot, full transmission of *P falciparum* is possible, the main vectors are anthropophilic and malaria is of a seasonal but stable type Except for the influence of control, annual epidemics would recur throughout the districts where there are suitable breeding places and with little variation from year to year Anophelism without malaria is unknown, *P falciparum* and *P vivax* are typically present in varying proportions, there has been no recession comparable to that in northern Europe, until recently no general control was secured, and all the characteristics of stability are evident The two most important vectors are *A sacharovi* and *A labranchiae* which overlap in Italy, the first being prevalent further east whilst the second species predominates in Italy and to the south and west of that country Their breeding places are similar, permanent and usually well vegetated water, with the consequence that malaria is often associated with swamps, springs and marshes, to which fact it owes its alternative name of paludism (L *palus*, gen *paludis*, a swamp or marsh) The normal range of flight of these mosquitoes is considerable, malaria being commonly transmitted within three kilometres of major breeding places and sometimes beyond that distance, while *A sacharovi* makes a prehibernation flight of 9 to 10 Km which is not, however, associated with the carriage of malaria

A superpictus is a subsidiary but still very important malaria carrier in the lands east of Italy, its local distribution is very much determined by its choice of breeding places, typically in cool moving water often free from vegetation, and best represented by the shingly river bed It is less anthropophilic than the two main vectors, feeding very readily on horses and cattle, and the malaria it conveys is unstable, occurring as severe epidemics varying greatly from year to year, transmission is more readily brought to

within the palaearctic region but is separated from an important part of it described later as the Mediterranean zone because the epidemiology of malaria is greatly different in the two parts

The normal brevity of the season and the coolness of much of it deters the multiplication of *P falciparum* which is rare in most parts of the area except southern China, *P vivax* being everywhere predominant and in many places the only parasite present. Malaria has been widely distributed within the area It has disappeared from most of Europe in a spontaneous recession covering a couple of centuries, to which reference has already been made, but the continued susceptibility of the area to endemicity has been demonstrated by many local outbreaks during the last two great wars Apart from these outbreaks, which have been widespread in central and eastern Europe and in Spain, the last remaining foci have been in the Danube Basin, in Holland, Portugal and Spain

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an end by cool weather, whether in terms of time, of altitude or of latitude, and is most feared in midsummer, in the warmer part of the zone, and near sea level There are a number of other vectors of less importance, *A claviger*, especially in towns where water is stored in cisterns, *A hispaniola*, which may carry a very unstable disease in Algeria and Morocco, and *A messeae*, under special conditions in Italy and the Balkans

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LEESON, H S, LUMSDEN, W H R, YOFE, J & MACAN, T T *Anopheles and malaria in the Near East* Memoir No 7, London School of Hygiene and Tropical Medicine London H K Lewis 1950

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and the following are of interest for their historical significance —

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A classical description of an attempt to eradicate an anopheline species in this zone is given in —

LOGAN, J A *The Sardinian Project* Baltimore Johns Hopkins Press 1953

(4) AFRICA AND ARABIA

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A great tract of northern Africa and Arabia is almost rainless, but rivers flow through it, there are springs and oases, and in parts there is an occasional rainfall feeding swamps or temporary streams, the water in which is often conserved to irrigate a little

land. Temperature would permit transmission through most of the year, but even where breeding places occur the usual dryness of the atmosphere militates against longevity of the mosquito and so against transmission. There are potential vectors in many places: *A. pharoensis* in the Nile Valley, *A. sergenti* in many of the oases in Egypt which are watered by springs, *A. multicolor* near saline waters on the coast, *A. hispaniola* in the extreme north-western parts which receive occasional rain and *A. gambiae* along its southern border. Doubtless owing to the dryness of the climate malaria is often confined to the more humid autumnal season and is generally unstable, with all the characteristics of that type. *A. pharoensis* conveys the least unstable type, a fact noticeable in nature and linked with its marked anthropophilism. Sporozoite rates are commonly very low, and the association of low values such as 0·3 per cent. with high oöcyst rates such as 6·7 per cent. indicates a very brief span of normal life, partly, perhaps not entirely, due to the climate. The oasis malaria carried by *A. sergenti* is very unstable indeed, often occurring in sharp severe epidemics between times of virtual freedom from malaria which mark the other side of the same picture. Malaria associated with *A. hispaniola* has much the same quality though coloured by the difference in its breeding places which are more temporary.

A. gambiae was found in 1942 to have invaded Egypt, having then penetrated along the Nile Valley to within 200 miles of Cairo and causing epidemics of unprecedented severity. It was eradicated from Egypt and from the northern parts of the Sudan by larvicidal campaigns and now only occurs along the Nile about as far north as Khartoum. It is the prevalent carrier to the south of the area where the Ethiopian region merges into the desert, and is responsible for such transmission as occurs in the southern desert parts. As with the carriers in the north, its longevity is limited by dryness of the atmosphere; on the whole it is a much less potent carrier here than in its proper sphere.

The eradication of *A. gambiae* from Egypt was followed by comparable and successful campaigns for the eradication of *A. sergenti* from some of the great oases in Egypt, first the Kharga and Dhakla Oases and later others, and there has been much

control of *A pharoensis* malaria in Egypt through residual insecticides A general control programme is in train in the Sudan, and between them these cover most of the malarious parts of the desert area which may well soon be substantially freed from the disease

THE ETHIOPIAN ZONE

This zone is roughly co-terminous with the zoo-geographical Ethiopian region Its malariological characteristics are set by the anophelines present, there are many more species of firmly anthropophilic anophelines in this area than in any other, some of them are widespread, in many localities they are numerous, and certainly some of the most prevalent are on the whole very long-lived Throughout much of the zone, temperature permits transmission through all or a large part of the year and adequate rainfall provides plentiful breeding places

The two chief vectors are *A gambiae* and *A funestus*, both widely distributed *A gambiae* is catholic in its choice of breeding place with a bias towards sunlit open pools and *A funestus* is associated with vegetated swamps grassy riversides and such-like water Their likes are such that except in dense forest there are few places where one or the other, if not both, are not prevalent Both are generally firmly orientated towards man breeding in his vicinity, biting him readily, and sheltering in his houses, though it has lately been realised that there are exceptions to this statement in the case of *A gambiae* It may be zoophilic and exophilic in some places, both its importance and its susceptibility to imagicidal control being then different from the normal as represented by the anthropophilic and house resting type The difference may lie in climatic factors certain temperature and humidity conditions may lead to an external and zoophilic habit, and it has been suggested but not proved that strains or races of the species may have different habits

Most measurements in both species in the equatorial zone show that anthropophilism is nearly complete There are reliable data on which to make estimates of longevity in many places, and throughout the equatorial zone it is considerable, daily mortalities

The prevalence of splenic enlargement does, however, indicate the intensity of infection to which the community is subject, and the spleen rate has become a traditional and still valuable measure of it

In later childhood and in adult life the enhancement of immunity continues, with a further decrease in parasite density and in the parasite rate, and a steady decline in the spleen rate The position then is apparently an exaggeration of that in childhood true freedom from infection is probably relatively rare though the demonstrable signs of infection become steadily less frequent Occasional bouts of intense parasitaemia occur but they are usually very brief, and survey will only show high parasite counts in a very small proportion of the people The decline in the spleen and parasite rates depends largely on the intensity of infection to which the people are exposed, being more rapid when the stimulus to immunity is great There thus arises a system of classification of endemicity, the most intense degree of which is represented by high spleen and parasite rates in the child associated with low values in the adult, the next degree is represented by high rates in both, and lesser degrees by lower values in both All of these degrees seem to the writer to run into one consecutive series There is, however, some convenience in classification which is harmless provided no emphasis is placed on the lines of division of categories That recommended by the First African Malaria Conference in 1950 recognised four types —

Holoendemic malaria, with a spleen rate in the 2–10 age group *constantly* over 75 per cent and a low spleen rate in adults,

Hyperendemic malaria, child spleen rate constantly over 50 per cent, adult spleen rate high,

Mesoendemic malaria, child spleen rate 11–50 per cent,

Hypoendemic malaria, child spleen rate 0–10 per cent

The first two of these names have come into common use and may well be adopted in a colloquial form, while the last two have not received any general acceptance and do not deserve it The classification was made in Africa and within that continent gives

a reasonable system of comparison but when applied elsewhere it may result in the false alignment of very different conditions

The clinical effect of these severe endemicities has been the source of much, often bitter, controversy One protagonist says there is no statistically significant evidence of high mortalities caused by the highest intensity, whilst the other says that the person who would measure them is the person who might prevent them and inhumanity has not extended to permitting deaths in order to ensure a proper diagnosis of cause Malaria control programmes, whether by drugs, larvicidal or imagicidal measures, do however, cause a very significant drop in the death rate particularly amongst young children It was shown in Freetown that elimination of the seasonal peak in malaria by larval control caused a reduction of 100 per 1,000 per annum in the infant mortality rate, and the same result was secured in the Belgian Congo by wide distribution of prophylactic drugs These findings are parallel to others from elsewhere and there seems reason to accept them as general Certainly some infants suffer severe clinical effects and some die, but the frequency of severe illness and of death falls off rapidly after the second year of life, giving way in childhood to disturbing but not necessarily distressing fever, and later to transient malaise It is probable that some degree of susceptibility remains throughout life, and it was noted in the war that malaria proved to be a common cause of fever even amongst those African soldiers who came from holoendemic areas and had never gone far from their homes It would be very difficult to deny that this degree of endemicity has always been connected with backwardness in economic and social progress, and to such an extent that the association has been included in an authoritative definition of hyperendemicity

The control of malaria in the Ethiopian region has had many setbacks It is very difficult to achieve by prevention of mosquito breeding and was not completely established even by a reduction of the room density of *A gambiae* to 0 03 in Freetown There has, however, been a partial sanitation of many areas by this method and both the routine control of *A gambiae* and the special control of *A melas* by tide management have been shown possible There

were early failures with residual insecticides, particularly in a systematic trial set up in Uganda and in experiments in Tanganyika which led to the belief that the *residual insecticides could not* control African malaria. The research which followed these failures has, however, shown the reason for them, the previous lack of appreciation of the interaction between some mud surfaces and insecticides which might lead to the inactivation of the latter and of the relatively very high mortality and therefore efficiency of insecticide needed to secure that end in Africa. The necessary daily mortality is probably often of the order of 65 per cent or even higher. An account is given elsewhere of the mortalities actually achieved by insecticides, from which it is clear that DDT may sometimes fail in adequacy, though a sufficient degree may be achieved by BHC and dieldrin. These conclusions have been substantially supported by practice in a number of schemes. Where endemicity is not extreme, as in the southern range of malaria in the Rhodesias and South Africa, normal programmes of control using *DDT have been as effective as elsewhere in the world* but they have sometimes failed in the central equatorial belt. However, BHC and dieldrin have achieved control and there are now remarkable schemes in the Congo, French Equatorial and West Africa, in Liberia and elsewhere.

It cannot be denied that there are difficulties in control in Africa such as are not met elsewhere and which must lead to that continent being behind the world in this respect. Prominent among them are administrational difficulties due to the poor state of *development of the country of government services, of communi*cations and other aspects of the background on which any programme must be built. Second is the very high endemicity which must be countered, and which demands a much higher and better sustained efficiency than is usually needed elsewhere, there follow the normal difficulties which may be encountered anywhere *including resistance by the insect*, and interaction of surfaces with the insecticide which plays a larger part in Africa than in places of more sophisticated housing conditions.

There is one point in which Africa may have the advantage. *P. vivax* is rare and *P. falciparum* predominates. While there is no

drug which can be widely distributed without medical supervision to secure the radical cure of vivax infections, there are such drugs available for falciparum infections It is conceivable that a combination of imagicidal control combined with simultaneous mass treatment might secure local eradication of malaria in a short time, and though it is not certain the *prima facie* case is sound enough as a foundation for pilot trials to elaborate and test it Preliminary work with pyrimethamine in the Congo and with amodiaquine in Indo-China lends encouragement to the idea, and is described in the section dealing with the role of drugs in control Extension of such programmes would demand the close integration of areas of action to build up a series of small schemes into one large one, and would need considerable administrative as well as technical experiment Success would, however, so materially reduce the ultimate cost of control that the effort would be more than justified

General epidemiological characters are described and well documented in —

WILSON, D B Malaria incidence in Central and South Africa Chapter 33, pp 800–809 in M F Boyd s *Malariology* Philadelphia and London W B Saunders Co, 1949

The following two papers describe surveys based on the present approach —

DAVIDSON, G & DRAPER C C Field studies of some of the basic factors concerned in the transmission of malaria 1953 *Trans roy Soc trop Med Hyg*, 47, 522–535

DAVIDSON, G Further studies on the basic factors concerned in the transmission of malaria 1955, *Trans roy Soc trop Med Hyg*, 49 339–350

and the following are local surveys of more than local significance —

WILSON, D BAGSTER Implications of malaria endemicity in East Africa 1939 *Trans roy Soc trop Med Hyg*, 32 435–446

BARBER M A & OLINGER, M T Studies on malaria in Southern Nigeria 1931, *Ann trop Med Parasit*, 25, 461–501

BARBER, M A & RICE, J B A survey of malaria in Egypt 1937, *Amer J trop Med*, 17, 413, 436

YOUNG M P & JOHNSON, T H (Jr) A malaria survey of Liberia 1949 *J nat Malar Soc*, 8, 247–266

Some of the problems of control can be studied in —

BRUCE CHWATT, L J *et al* *An experimental malaria control scheme in Ilaro* Malaria Service, Department of Medical Services Federation of Nigeria Information Bulletin No 3 1955

FEUILLAT, F *et al* Progres recents dans la lutte anti malarienne au Katangu 1955, *Ann Soc belge Med trop*, 33 621–655

(5) SOUTH AND EAST ASIA

South East Asia includes most of the oriental zoo-geographical region The greater number of incriminated vectors and the great variety of types of epidemiology encountered make description as a whole impossible, while description in terms of individual countries produces artificial distinctions and results in a tiresome catalogue The area considered, however, comprises four climatic zones differing radically from each other and corresponding approximately to the distribution of particular vectors and types of epidemiology The rough boundaries of these zones are shown on the map in the endpapers

The greater part of India, Ceylon, East Pakistan, and the countries on the shores of the Persian Gulf experience a true monsoon climate characterised by a sharply defined seasonal rain fall limited to a few of the summer months during which the precipitation is not heavy, being usually below a total of 50 inches

To the east of this area is a great mountain mass comprising part of the Himalayan foothills, Assam, and the hills of Burma Thailand Indo China and the southern provinces of China in which rainfall is spread over a considerable part of the spring summer and autumn months and is for the most part heavy though there are relatively arid regions in the upper part of Burma and the Shan States This country is radically different from that of the true monsoon area and its anopheline fauna differs correspondingly

The third area lies further south and east, it has an equatorial oceanic climate with little annual variation in temperature and prolonged rains over much of the year It includes Malaya

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Indonesia, Borneo and the Philippine Islands, and also the coastlands of a part of India, Burma, Thailand and Indo China In these coastal districts the climate is oceanic and the picture of malaria in them from Hong Kong round to the mouths of the Ganges corresponds to that in the Last Indian islands

The fourth area to the north east includes part of China, Korea and Japan It is well out of the true tropical zone, experiencing a seasonal climate with marked range of temperature and a fairly general distribution of rainfall

INDO PERSIAN ZONE

This zone, numbered 8 on the map, covers the distribution of *A culicifacies* and *A stephensi* which between them determine the general pattern of malaria as it affects the densely populated plains Within this area there are large hill tracts where the pattern is predominantly set by *A fluviatilis*, and lesser vectors may aid them in some places, notably *A annularis* in the coastal parts of Madras and Kerala (Travancore) and *A varuna* in the hills of Orissa The other great vectors in India, *A philippinensis* and *A sundaicus* in Bengal and *A minimus* in Assam, are largely outside the zone, in those described as the Malaysian and the Indo Chinese hills respectively, but to some extent overlap into this zone on the north eastern border, the range of *A minimus* stretching along a considerable part of the Himalayan foothills

A culicifacies is by nature a strongly zoophilic species anthropophilic indices are usually low, of the order of 10 to 15 per cent, and one of 2 5 per cent was recorded in a considerable series in Madras It apparently turns to man only when cattle food is relatively hard to come by, but under these circumstances may perforce feed chiefly on him In towns the species is thus deviated to man, and the evidence of the very high sporozoite rates recorded in a Sind epidemic by Covell and Bailey shows it must there have fed almost exclusively on him Although widely distributed over the hot plains of India it is not fully adapted to high temperatures and survives best at temperatures well below the summer normal of most of India Its expectation of life during the malaria transmission season is short, direct measurement and the evidence of

relative sporozoite and oocyst rates in many areas indicate that the daily mortality may often exceed 20 per cent, though in the cooler weather at the end of the transmission season in north India the rate may be much less. The critical density of this mosquito is high. Factual observation in Madras indicated that it exceeded catching 10 per hour, while deductions from its length of life and zoophilism suggest that in some areas it may be of the order which would result in 5 bites per person per night. Its index of stability is extremely low, of the order of 0.1. It rests in cattle sheds and houses, has a limited range of normal flight not exceeding 1 Km, and typically breeds in pools with or without vegetation chiefly in those which have held water for some time rather than purely temporary ones. It is thus common in pools in river beds in borrow pits, in pools formed by seepages and in village tanks. It may breed in gently moving water of irrigation canals when vegetation gives it anchorage. The type of breeding place favoured is often produced by light rains rather than heavy and this species does not occur, or is rare, in places of extreme rainfall. It is thus absent from the south western parts of Ceylon and from some of the coastlands of western India.

In contrast to this species *A. fluviatilis* is usually highly anthropophilic, though there is some suggestion that there may be two races in north and south India, the former being less anthropophilic than the latter. The evidence of relative sporozoite and oocyst rates suggests a normal considerable longevity, and the critical level has been factually recorded as very low, of the order of catching 1 per hour. It is probably expressed by a density below 0.1 and nearer to 0.01 in relation to human density. The index of stability is high and probably usually exceeds 6. It rests chiefly in houses and has a limited range of normal flight of about 1 Km. It breeds almost exclusively in moving water in streams and rivers regardless of the presence of marginal vegetation, so that it may be found in profusion in the backwaters of rivers as well as in minor streams. It also occurs in apparently standing water supplemented by seepage as in rice fields immediately below hills. This breeding habit restricts the species to hills and foothills in contrast to *A. culicifacies* which is similarly virtually restricted to

plains, so that throughout most of India these two species are complementary to each other, the one or the other usually being present, but rarely the two

A stephensi is essentially a zoophilic species and in rural surroundings—where an anthropophilic index of 1 4 per cent has been recorded—probably feeds very largely on animals In such places it has little influence on malaria but it becomes important when it is deviated to man by the absence of cattle It is the only oriental vector fully adaptable to urban life and can multiply in the centre of large cities such as Bombay, where it is perforce deviated to man and becomes a dangerous vector Under normal conditions its critical density is very high and index of stability low

A varuna to some extent resembles *A fluviatilis* It is highly anthropophilic and probably long-lived, it breeds more commonly than *A fluviatilis* in apparently stagnant water and usually in the presence of vegetation Though its total distribution in peninsular India is broad the areas which it influences are smaller than in the case of the two main species

The epidemiological characteristics of malaria in this area are determined by the seasons, the climate, and the local factors determining the presence of breeding places for one or other of the species Throughout the areas influenced by *A culicifacies*, which are chiefly the plains of India, malaria is extremely unstable and characterised by great variations in incidence A progressive decline has certainly been occurring over the last 70 or 80 years in the Punjab, but it is marked by an epidemic periodicity over an eight-year cycle, the outbreaks sometimes being of the most dramatic severity, the epidemic of 1908 stimulated pioneer research by Christophers which is the basis of our knowledge of epidemic happenings A similar marked periodicity sometimes rising to disastrous epidemics, as in 1934–35, occurs in Ceylon Between these two main epidemic foci the disease is very variable and there are smaller places in central India liable to dramatic happenings—in Madhya Pradesh, Andra Pradesh, Sind, and Rajasthan, similar outbreaks have also occurred in Kerala, though they have not been properly documented The mechanism of these periodic epidemics has been the subject of much study by Gill,

Briercliffe and Rajendram and Jayewickreme. There is always some periodic oscillation, but when favouring climatic conditions coincide with the natural period, fulminant outbreaks occur In northern India the favouring climatic conditions are prolongation of the monsoon by early rains, and rainfall before the actual monsoon providing an opportunity for preliminary multiplication of the parasite The operating mechanism is thought to be a prolongation of mosquito life by reason of the increased humidity associated with unusual rainfall, but it seems very probable that a prolongation of the season beyond its normal of under two months in the Punjab also operates by giving time for full development of the epidemic In Ceylon periodic epidemics are accentuated by drought followed by light rain which together lead to the production of ideal breeding places for *A culicifacies* Examination of the records of many of these epidemics in Ceylon suggests that though this mechanism is chiefly responsible for outbreaks occurring in the spring months, some of those occurring in the autumn are considerably favoured by excessive rainfall and probably through the effect of humidity on mosquito longevity

All degrees of severity are found in this zone Anophelism without malaria is well acknowledged and occurs in many parts of eastern India In some places normallv free from malaria there may be occasional recrudescences when conditions are particularly favourable The detail of such recrudescences in central India was described by Viswanathan, and the outbreaks of malaria following the construction of the Cauvery Canal system were of the same nature In places where the critical level is first exceeded malaria may reach all degrees of severity, and north-eastern Ceylon was depopulated some centuries ago by such fresh establishment of malaria The characteristics of malaria in such areas, though conforming to definitions of hyperendemicity, differ from those seen in places of stable malaria, and particularly by the occurrence of great fluctuations in endemicity and the failure of acquisition of complete immunity by the adult population

Both Ceylon and India have started programmes which aim at gaining complete control of the disease, that in Ceylon accepted the object of total eradication as early as 1954, while that in India,

with very much larger populations to cover, is still concerned with the primary object of full control A national malaria programme was formulated and has been incorporated in two successive Five Years' Plans It is based on major pilot trials, prominent amongst which was that in Bombay, and the successive formation in more or less military manner of control units each capable of undertaking the protection of about a million people, and nearly 200 of which were in the field by 1956 When this programme is complete the object of eradication is to be reviewed In Iran there is also a national programme and in Pakistan major schemes have been started especially in the epidemic areas around the capital, Lahore The total size of these schemes is enormous and covers very large populations Their final outcome is still to be foreseen but there can be very little doubt that they are at least radically altering a picture which may soon be chiefly of historical interest

THE INDO-CHINESE HILL ZONE

This region extends through the hill land from the Himalayan foothills in Uttar Pradesh to southern China, and southward to the limits of the hills in Burma, Thailand and Indo-China Within this area which is numbered 9 on the map the malarious zone extends to over 6,000 feet The characteristics of malaria are determined by those of the principal vector *A minimus*, and the main subsidiary *A leucosphyrus* Both of them are highly anthropophilic There is good evidence that *A minimus* is not readily deviated to cattle and that it is normally long-lived The transmission season is long, more than 6 months throughout most of the area and perennial in some parts of it Both of the main vectors are highly selective in their choice of breeding place, *A minimus* selects cool water with marginal vegetation which is to be found in summer in open sunlit streams and seepages, and in winter in a much larger variety of water types *A leucosphyrus* is restricted to dense jungle and forest areas, breeding in deeply shaded pools and seepages These breeding requirements are not universally met and in consequence in some hill areas the population lives free from the disease The clearance of forest from these areas almost

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inevitably produces breeding places for *A. minimus* so that developed regions are almost always very malarious. Other minor vectors may play a part in transmission from time to time, *A annularis* and *A maculatus* having been locally incriminated, and it is probable that further work would incriminate other species in particular places.

Malaria transmission is intense and varies little from year to year. *P falciparum* is the principal parasite observed, *P vivax* and *P malariae* having very subsidiary importance, probably due to the acquisition of resistance by the population. The normal picture of stable malaria is seen, the parasite rates and spleen rates in infants are high but amongst adults they are low; the full clinical effects of malaria occur amongst infants but not amongst older children and adults. The effects on the people have been particularly studied in Indo-China where they have been shown to resemble those in Africa. It has also been shown that the resultant total mortality of the population is high, and that the social effects of the disease definitely restrict the population to a primitive condition. There has been a considerable plantation development in a part of the area, Assam, to which country many labourers have migrated from elsewhere in India. Amongst these people the morbidity and mortality were high before deliberate control measures were undertaken, and many of the principles of control have been developed in this country. It was for long attempted by the prevention of breeding and considerable but never complete success was obtained before the substitution of attack on the adults by residual insecticides. Even with these insecticides full success has not been universally achieved and the position seems to resemble that in Africa in that the mortality normally obtained by the use of DDT is no more than just sufficient to control transmission, which continues if there has been even minor impediment, such as the use of slightly unsuitable preparations or failure to treat a sufficiently high proportion of houses.

THE MALAYSIAN ZONE

This zone, numbered 10 on the map, comprises Malaya, Indonesia, Borneo, the Philippine Islands and the belt of coastal

plains from South China to Bengal Epidemiological conditions are nearly the same throughout it The temperature is perennially, or very nearly so, adequate for transmission of both *P vivax* and *P falciparum* Rainfall is considerable and humidity high, and in consequence conditions are ideal for breeding and long survival of many species of mosquito It appears that only one of these, *A leucosphyrus balabacensis*, has the characteristics of anthropophilism and longevity necessary for the transmission of stable malaria, and this species has a limited distribution It is a forest mosquito associated with dense shading vegetation and so is not seen in developed agricultural areas, and has only been incriminated as an important vector in the forested parts of Sarawak and Borneo Full data on which to define the feeding habits and longevity of the other vectors of malaria is lacking but it appears that they are mostly zoophilic, and the malaria they convey is of a very unstable type Atmospheric and breeding conditions are so favourable for the maintenance of anopheline populations that a considerable number of species which might not be capable of transmitting under less favourable circumstances act as vectors They include *A sundaicus*, *A maculatus*, *A hyrcanus sinensis*, *A novumbrosus*, *A aconitus*, *A minimus flavirostris*, *A philippinensis* and *A barbirostris*

The species of most general importance is *A sundaicus*, restricted by its preference for saline water to coastal regions, but prevalent in coastal swamps throughout the whole region except the Philippines It is associated with severe epidemics of malaria which are almost always, however, intermittent, some separated by periods of virtual freedom and others by times of low transmission Precipitin tests indicate that it is anthropophilic but it has been suggested on the basis of field observation that it is normally short lived, which would explain the very marked instability of the malaria with which it is associated

A maculatus which breeds in sunlit streams and seepages, is the principal vector of the hill areas of Malaya and Indonesia and has been incriminated elsewhere as a local carrier It is essentially zoophilic and may have an anthropophilic index as low as 3 per cent It is also probably fairly delicate and may be less long-lived

than some other species In places where cattle are kept and a mixed agriculture is practised it transmits an unstable variety of malaria characterised by epidemics but also by frequent anophelism without malaria It is, however, readily deviated to man when cattle are not present and the anthropophilic index may then approach 100 per cent Such deviation associated with the multiplication of breeding places occurred on a very large scale during estate development in Malaya and Indonesia, with the resultant temporary production of a stable form of malaria The settlement of estates and perhaps particularly the increase in numbers of cattle has generally allowed it to recover its more typical habit of zoophilism and the unstable form of malaria is now replacing the stable

A hyrcanus sinensis frequents a different type of breeding place, typically exposed standing water as in rice fields, and it is therefore prevalent in a different type of country from *A maculatus* but otherwise it has very similar characteristics, recorded anthropophilic indices vary from 1 to 73 per cent, their values apparently depending largely on the numbers of cattle available as a source of food There are many extensive areas infested by this species which are entirely free from malaria, but in some places, notably in Indonesia, its density is often sufficient to maintain transmission, typically in the form of recurring epidemics or a very fluctuating endemicity of both *P falciparum* and *P vivax* The fact that transmission is never as intense as in the areas of *A gambiae* or *A minimus* is shown by the failure of adults to gain full immunity Experience has shown that reduction in numbers of the species can readily limit transmission which is also abruptly ended by the use of residual insecticides *A novumbrosus*, *A aconitus*, and *A barbirostris* have limited significance as vectors in isolated areas of Indonesia, in Malaya and possibly elsewhere *A aconitus* and *A barbirostris* resemble *A maculatus* in that they are essentially zoophilic but may be deviated to man, under which circumstances they become vectors *A novumbrosus* is restricted to forest areas and so can have little significance in developed country at its extreme periphe T e ole record of precipitin reactions gives a *h* *opo* of 95 per cent, but

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A minimus flavirostris is the principal vector of the Philippines It differs radically from the type form in that it is essentially zoophilic Its breeding places resemble those of the type form, and in consequence of these characteristics the malaria it carries in the Philippines is irregular in distribution and unstable in character, endemicity being sometimes high but with a tendency to fluctuate, and the disease is fairly readily controllable by attack on breeding places or on the adult mosquito Considerable trials of control of malaria by agricultural means, leading to reduction of suitable breeding places and deviation to cattle, have had some success, and it seems probable that further development along these lines might well provide an ultimate protection against malaria carried by this mosquito Such methods must however, be slow in development and application, and could not be made generally effective for many years, whereas control by insecticides can be immediate and fully effective The Philippine Government has undertaken an eradication programme based on the use of these insecticides, to which the methods of biological control form a background

A philippinensis is known to be an important vector only in Bengal and throughout the rest of its range it does not act as a carrier Though it rests in houses it is zoophilic, an anthropophilic index of 6 4 per cent has been recorded It appears that a century ago it was not of great significance even in Bengal malaria having developed into an important problem only following the multiplication of roads and railways and changes in the rivers leading to great increase in breeding of this species There are still areas of anophelism without malaria and the disease it carries is typically unstable and readily amenable to control

THE CHINESE ZONE

This includes a part of China up to southern Manchuria, Korea and the southern part of Japan It merges gradually into the Indo-Chinese Hill Region, the characteristics and vectors of which extend some way into China itself The season is relatively short

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and the climate is unsuitable for transmission for cert[illegible] parts of the year. The princip[illegible] which [illegible] e bu[illegible] s tra[illegible] [illegible] may be very prevalent. [illegible] in the great rice-growing seasonal, *P. vivax* being very common. The associated disease is rare. In the northern part of the zone and *P. falciparum* relatively *hyrcanus* and it is supplemented in some places by *A. pattoni* replaces *A.* Little is known of the characteristics of the mosquitoes in this *A. sacharovi.* region or of the epidemiological types of malaria encountered, but it may well be that *A. sacharovi* as in Europe is anthropophilic and it is unlikely that malaria would be maintained in the northern part of this region unless this was the case.

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WORLD HEALTH ORGANIZATION *Malaria Conference for the Western Pacific and South East Asia Regions* W H O Technical Report Series No 103, 1956

For numerous and detailed studies of malaria in this region the reader is referred to the volumes of the —

Records of the Malaria Survey of India 1929–1937
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which between them constitute a continuous series

(6) AUSTRALASIA AND THE PACIFIC

The Australasian region is sharply demarcated from South-East Asia or the Oriental region as there is a complete break between their fauna, including the anophelines The dividing line runs to the east of Celebes Island and to the west of the Moluccas, Seram, and Timor In the north-east, east and south of the region there are great non-malarious areas Freedom from malaria in the Pacific region is due to the absence of anophelines, in Australia itself the poor vectorial capacity of the prevalent anophelines and the dry climate have led to the disappearance of malaria from all except the northern parts of the continent

AUSTRALASIAN ZONE

To the north is a great archipelago which includes the Moluccas, some lesser islands between the Moluccas and Celebes Island including Soela and Peling, the great island of New Guinea, the

Bismarck Archipelago, the Solomon Islands and the New Hebrides, together with all the smaller islands included in this area The climate is perennially warm, the rainfall is considerable and evenly distributed, and the humidity is normally high In consequence the climate is almost ideally suited for the perennial transmission of malaria, and the disease is limited only by the rarity of breeding places on some islands where the soil is very porous and water accumulations are infrequent

The biggest island, New Guinea, is only partially explored and its malarial characteristics are not clearly known It appears, however, that malaria is widespread except in the mountains, and that it is usually of a stable type, resembling that in the African region and stimulating the production of a firm immunity in adults Some mountainous parts of the island have, however, been free from malaria, or suffered little from it, and communal immunity is here non-existent or poor The process of development is, however, leading to the introduction or extension of malaria in some of these places with the production of epidemics Though ultimately these might be restrained by immunity, the process would be slow, and control is a necessary corollary to economic advance

The stability of the disease in New Guinea and some other parts of the zone is determined by the characteristics of the main vector *A punctulatus punctulatus* which is highly anthropophilic It is to some extent supported as a vector of the disease by *A punctulatus farauti* which, though closely related, is zoophilic, and when alone transmits an extremely unstable type of malaria as in northern Australia itself These two carriers may be reinforced by others when local conditions are particularly favourable to them They are *A annulipes, A bancroftii, A subpictus, A amictus* and *A amictus hilli* The two principal vectors are pool breeders and have a particular tendency to breed in domestic pools around habitations, including car tracks and hoof marks In consequence they are extremely common in the islands where the rainfall is heavy and the soil will retain water as pools In some islands the soil is porous and pools are rare, breeding is then scanty and malaria may be less severe *P falciparum* predominates throughout the entire zone though both *P vivax* and *P malariae* are fairly widely distributed

In Australia itself the epidemiological picture is different from that in the islands Except in the northern part of Queensland the climate is dry and the temperature has marked seasonal variations Malaria is limited almost entirely to north of latitude 20° S, occurring in the northern parts of Queensland, the Northern Territories and Western Australia A marked epidemic character with both major and minor waves has been observed for many years A relatively large wave ended at the close of last century, since when the disease has decreased rapidly, though with local exacerbations, some of which have been due to climatic changes and others due to the constant migration of miners from the mining districts of New Guinea to those of Australia The characteristics of epidemics have been greatly affected by the extreme sparsity of population and consequent increased difficulty in the spread of epidemics from place to place, nevertheless once arisen they have tended to diffuse over great areas of the country It is possible that *P falciparum* may have been the principal parasite in some of the epidemics in the early part of this century, but all of those recorded latterly have been due primarily to *P vivax*, *P falciparum* being rare or absent The last of these epidemics was in the neighbourhood of Cairns in 1942, since which time the disease has continued to decrease until the numbers of cases now recorded in the continent are extremely small This evanescent malaria with intermittent epidemics principally due to *P vivax* is typical of the highly unstable disease, which does not penetrate into the central or southern parts of Australia where the season is abbreviated

The evanescent nature of the disease has made the demonstration of sporozoites in any species of mosquito very difficult It has, however, been established that *A punctulatus farauti* is the main vector in northern Queensland and it is assumed on epidemiological grounds that it has also been the main carrier in other parts of northern Australia It has been suggested but not substantiated that other vectors might play a part, the species brought under suspicion being *A annulipes*, *A bancroftii* *A amictus*, *A amictus hilli* and *A meraukensis*

There has been much concern at the possibility of the establishment of malaria in central and southern Australia The measures taken to prevent it have largely taken the form of attempts to prevent importation of gametocyte carriers and their treatment when detected, much effort having been expended to this end amongst soldiers returned from the Pacific war It seems, however, improbable that the disease could be established to any serious extent so long as the anopheline fauna remains as it is at present Temporary epidemics might occur round foci of imported gametocyte carriers, but analogy from other malarious areas suggests that they would rapidly die out even in the absence of deliberate control measures A very much greater danger to Australia would seem to be the importation into it of *A punctulatus punctulatus* which might well be a tragedy equal to the importation of *A gambiae* into Brazil If it found climatic conditions suitable for its survival it is probable that it could transmit malaria of a highly stable type in the northern parts of Australia, and that the epidemics could extend to the more humid coastal areas of central and possibly even southern Australia

THE PACIFIC ZONE

The Pacific zone includes almost all the islands in the Pacific Ocean to the east of a line which starts in the Ogasawara Archipelago or Bonin Islands at about 27° N and 142° E, thence runs southwards to the north-western point of New Guinea, eastwards along the equator to near the Gilbert Islands, then southwards and westwards again to leave the New Hebrides on its west and New Caledonia and New Zealand on its east The zone extends eastwards from this limit to near the coast of South America and includes in that region the Galapagos Islands and Juan Fernandez Islands at 33° S and 80° E The zone is free from malaria, owing to the absence of anophelines which might act as vectors The risk of importation, particularly by air, is clear Strict measures are needed and are taken to avoid it by the disinfestation of aircraft and the sanitation of airfields to make their surroundings inhospitable to any anophelines which might be imported The risk cannot, however, be totally eliminated and they might become established

within the zone Experience elsewhere suggests that if this were to happen epidemics would result, but possibly after a lengthy period, perhaps amounting to some years during which appropriate preventive measures could be taken

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CHAPTER VII

THE MALARIA SURVEY

THE term 'malaria survey' has come to describe almost a discipline in itself, in which many studies of entomology, parasitology and ecology have become traditional, often without relation to their immediate value. A survey is, of course, properly a strictly applied art in which subjects are taken up and discarded as they are found useful or outworn, and it should include just those procedures needed to understand epidemiological happenings or the problems of control as the case may be. For the purposes of control the problems may be few and in some cases schemes can be carried out largely on the basis of existing local and general knowledge, though they can always be refined and perhaps made more economical by special studies.

The description which is given here includes the procedures which would be needed to give a complete epidemiological picture as a valid background to understanding happenings and initiating control. They would give the information needed in a terrain which was previously unknown in this respect, whereas much of the information is available beforehand in most places. Some procedures are novel to the standard conception of a malaria survey but to balance this there are many items of the standard which have been omitted.

A proper appreciation of epidemiology requires knowledge of the transmission season, of the vector, its density by seasons or at least at the time of greatest transmission, typical sporozoite and total infection rates, the vector's man-biting habit and some expression of its longevity, with knowledge also of the prevalence and condition of malaria as shown by the infant parasite rate and a study of past happenings. If these are to be elaborated for epidemiological studies it is best done by gametocyte rates and especially gametocyte counts in infants and young children. The inclusion of spleen and parasite rates can give some help but

serves largely to translate valuable information obtained from the foregoing data into traditional but less informative terms

The epidemiological picture derived from this information needs expansion, if it is to form the basis of control, by a preliminary reconnaissance of the resting and breeding places of the vector, followed by a detailed study of either one or the other as imagicidal or larvicidal measures may seem appropriate If imagicidal measures are to be undertaken there should be an associated study of the mortality achieved by insecticides applied under local conditions and on local materials, and of the susceptibility of the vector to the insecticide

A number of examinations of local conditions may be necessary after these studies in order to appreciate the supply, transport, and administrative problems of control, their nature will depend on the method of control chosen and on local conditions As a preliminary to residual insecticide programmes information would be required on population, its arrangement in villages or otherwise, the common type of house, the average number of occupants and the internal surface area, the nature of other mosquito resting places, the quality of roads and tracks, and the convenience of supply points on railways or other main routes, together with other such-like matters Before larvicidal work is undertaken much mapping of incriminated types of water is needed with assessment of their areas, classification of their nature and appreciation of the transport and administrative difficulties involved in treating them

SEASON

The possible limits of the transmission season may first be judged from examination of meteorological data, transmission being unlikely when the mean temperature falls below 18° C, and probably slight except when it is over 21° C Within the broad limits given by temperature transmission may be determined, at times decisively, by other factors The only sure guides lie in the times when sporozoites can be found in active mosquitoes and when infections appear in infants not previously exposed Morbidity statistics alone may be most misleading because

epidemics of relapses of vivax malaria may occur when transmission is absent If caution is used to avoid such pitfalls morbidity figures may be helpful, provided that it is remembered that a seasonal rise starts some time—perhaps 2 to 4 weeks—after the first transmission occurs and may be brought to an end by the processes of immunity before transmission ends

INCRIMINATION OF VECTOR

The vector can only be fully incriminated by demonstration of sporozoites in the salivary glands of wild-caught specimens, and no species can be cleared of suspicion until many thousands have been dissected and shown to be negative The simple capture of specimens in houses and their dissection provides much evidence, but there are pitfalls even in this It cannot be assumed without reason that the vector is to be found in the houses in the daytime, or perhaps at any time *A leucosphyrus* was long overlooked as a carrier through making this assumption Some catches should be made at night, and outdoor biting anophelines need consideration A mosquito such as *A aquasalis* may be the actual vector but for long defy incrimination by detection of sporozoites, the very small proportion of infective mosquitoes being counterbalanced by the enormous prevalence of the mosquito which thereby sustains transmission Incrimination in such a case may turn partly on circumstantial evidence, partly on the demonstration of immature but developing parasites in nature, and the happening of full development in specimens cared for in the laboratory Moreover, sporozoites may be of other than human species of malaria parasite—several species of outdoor resting mosquitoes have been found heavily infected with sporozoites of non-human plasmodia Circumstantial laboratory and field evidence must therefore be taken together to build up a firm case against a vector

There is already a considerable accumulation of evidence on the vectors in most countries, which can provide very useful guides, to be accepted critically and examined with reference to local conditions Some main vectors are mentioned in the chapters on local characteristics, but it is to be remembered that one described as of minor importance in a continental context may be very

important in the context of some smaller area, and local study is therefore essential

The relationship between the sporozoite rate and the total mosquito infection rate is closely dependent on the longevity of the insect, which may be quite reasonably assessed from it Examination for sporozoites should therefore be amplified by careful examination for oöcysts, and three rates—oöcyst, sporozoite and total infection—should be recorded This clashes slightly with the desire to dissect as soon as possible after capture, when the stomachs of many mosquitoes may be distended with blood and unsuited to examination The error introduced into the sporozoite rate by a few hours' delay is, however, small and justified by the additional knowledge gained, while an allowance could be made for it from that additional knowledge to restore precision if it were needed

MAN-BITING HABIT

A mosquito does not bite at random but in accordance with a periodically recurring hunger and in response to stimuli, admittedly only poorly known, which direct it towards particular food sources Hunger of the female for blood is closely connected with the initiation of egg development, the frequency of which depends on temperature which largely determines the rate of growth These rates and frequencies vary with species but, at tropical temperatures exceeding about 24° C, *A gambiae* and perhaps many other species feed on alternate days, whilst in cooler weather the interval is lengthened to 3 days or even more

Attraction to a host may take the form of a strong inclination towards man, towards other animals to the exclusion of man, or may be more general so that different mammalian sources seem to be selected in proportion to their availability Determination of the habits of a vector can only be through identification of blood meals by the precipitin test combined with observation of the alternative sources of food available at the time the collections were made

Such examinations need repetition in different localities, for habits may vary from place to place in accordance with variations

in climate, the availability of cattle, or other unknown factors The task involved may be considerable, but studies should be made on a bigger scale than has previously been practised as a routine Food preference is one of the two most important factors influencing transmission and its control, the trouble is less than that involved in many routine practices of very doubtful value and techniques of sufficient accuracy can be followed in very simple laboratories

The man-biting habit is a compound of frequency of feeding and choice of host It is often referred to here, and indicates the probability that a mosquito will feed on man during one day, for which the symbol *a* is used Thus if a mosquito fed on alternate days (average 0 5 times per day) and 30 per cent of its feeds were on man, it would be said that the man-biting habit was 0 15 (i e 0 5 × 0 3) A mosquito must of course bite man twice before it can transmit infection, and transmission varies with the squared value of the feeding habit which constantly recurs in mathematical expressions as a^2

The technique to be used for performing the precipitin test depends on the intention with which it is done The malariologist may wish only to know whether the mosquito feeds on man or not, having perhaps little interest in the alternatives chosen, and for him a simple test which can be carried out in any laboratory will suffice The entomologist engaged on special studies may wish for much more—to know what animal was chosen as an alternative, and he may wish to refine this information by identification of species of host and not merely of families or larger groups The techniques for this precise identification have been but recently developed, they include elaborate processes requiring a serologist's full skill, and they cannot therefore be carried out except in special laboratories The value of this sort of precision to the entomologist can be considerable, but the possibility of its attainment should not distract attention from the great enrichment of knowledge which can be gained from simple tests which can be carried out in simple laboratories, and which answer the question—man or not?—with sufficient precision for the malariologist's purpose For either process the methods of

collection and preservation of materials are the same, and they are described together with a simple technique of the test in Appendix II

LONGEVITY

The density of vectors, their numerical prevalence in relation to that of man, is the most difficult of all factors to measure with any precision, but to compensate for this there is usually no necessity for precision, a reasonable estimate of density at the season of greatest prevalence sufficing, and indirect approaches may be used An estimate of the typical number of bites received by an individual in one night is quite enough if it is remembered that this represents the density multiplied by the biting habit, a suitable correction being simple if the latter is known In the case of species which bite indoors a figure for the average number per room corrected for the frequency of biting and the average number of occupants is enough for any routine purpose, though the precision of entomological research may require special techniques of trap huts and outdoor collection This density in relation to that of man is given the symbol m, which frequently recurs in mathematical expressions, often in conjunction with the square of the biting habit as ma^2

Mosquitoes die from many causes, old age is one, delicacy in extreme youth is probably another, but the principal causes of death are almost certainly hazards of daily life falling equally on those of all ages They vary from time to time and especially with climatic conditions, so that any precise statement of anopheline mortality would be impossible except in relation to some particular place, time, and age group The study of many laboratory colonies, and of several populations in the field, leads however to the conclusion that it is reasonable in any area to designate a mortality rate representing an average Moreover, the weight of evidence shows that it is reasonable to look on mortality as falling equally on all age groups, such deviation from the average as there is with age being insufficient to upset the picture Mortality rates are best considered in their converse form, as daily survival rates, because survival makes transmission possible Hence the

probability of survival through one day, always a figure below 1 0 such as 0 9, figures largely in mathematical expressions as p It is of such importance both in the theory of epidemiology and in that of control that some attempt should be made to measure it.

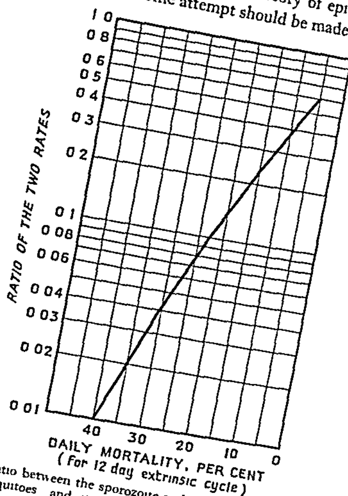


Fig 10 The ratio between the sporozoite and the total infection rates in mosquitoes and its relation to their longevity

The effort has only recently been made in response to the development of mathematical theory and there is still much room for development, though the techniques which have been used have given very consistent results Direct observation of laboratory colonies can be misleading because all members of the colony are exposed alike to one set of hazards, changes of microclimate from which they can make no escape, and protected alike from another set, predators, which may be important in nature Direct observation in nature has so far proved impossible, and

there remain only indirect approaches which may, however, be very valuable

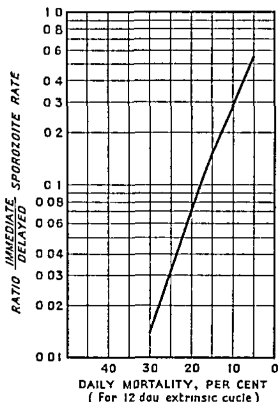


Fig 11 The ratio between immediate and delayed sporozoite rates and its relation to mosquito longevity

Indirect approaches depend on the fact that a reasonable estimate can be made of the probability of survival if that proportion of a population which is below, and that which is above a particular age can be recognised The search for a method turns on recognising some dividing line separating age groups If a characteristic could be found such that all anophelines showing it were above a definite age and all those without it were below, the task would be easy Alternatively if two characteristics can be found such that all showing one are above a certain age (though those without it not necessarily below that age) and all showing the second are above another age (again those without it not necessarily below this other age) and the chances of acquiring the characteristics are equal, then a good estimate can be made of longevity

This last might seem too much to hope for, but is in reality ready at hand to the malariologist A mosquito with visible oocysts either alone or together with sporozoites is, in most climatic conditions, at least three days old, and one showing sporozoites is, for the same conditions, at least twelve days old It follows that the ratio of the sporozoite rate to the total infection rate gives a guide to the probability of survival, illustrated in graph form in Figure 10 and given mathematical expression in Appendix I The graph necessarily refers to one set of climatic conditions where sporozoite development lasts twelve days, but its use for quite widely different ones will not introduce serious error because development of both characteristics, oocysts and sporozoites, is similarly affected by climate and the ratio remains much the same whatever the speed of development

The ratio between immediate and delayed sporozoite rates, the latter being taken after preservation of the insects for about twelve days, can give equivalent information and this has proved very valuable in the field A mathematical expression (69), is given in Appendix I and the relation is illustrated in Figure 11 This refers to rates separated by an interval of twelve days and is applicable whatever the actual length of the extrinsic cycle

These two techniques have proved practicable and are valuable, but fail in one way they depend on the prevalence of malarial infection which it is the malariologist's object to prevent Other approaches are necessary Davidson has developed a technique based on measurements of the ampulla of the oviduct in a sample of the anopheline population, and described in Appendix II Gillies has more recently described a means of recognising the proportion of an anopheline population which is nulliparous, and therefore below a certain age Though his technique is young it may well prove a valuable additional tool which will be complementary to that of Davidson

Measurement of longevity is still immature, it undoubtedly deserves much further exploration of technique and new methods, including study of mosquitoes tagged with radio active material will probably be developed

The probability of survival through one day recurs in almost all relevant expressions, where it is designated by the symbol p, but rarely in its simple unqualified form A common form is the probability of survival through n days, or p^n, and another is the expectation of life of the mosquito, or $1/(-\log_e p)$ The values of these expressions for different values of p and n can be read off from Table 1, no special calculation usually being needed as intermediate values can be interpolated graphically

RESTING HABITS

Study of the resting habits of mosquitoes has assumed increased importance since the introduction of imagicidal methods of control and there are still many gaps in our knowledge, particularly because some preconceptions on the subject have been proved false by the present practices of control There are three types of resting place to be considered houses, cattle sheds or other man-made shelters, and outdoor resting places For many purposes the first two could be grouped together except that distribution between them indicates where insecticides should be most vigorously applied

Indoor resting places are easy to identify, outdoor ones are harder to study Some light may be thrown on the proportion of time spent indoors and outdoors by study of the developmental state of those indoors, for if substantial groups such as those with developing eggs are disproportionately few, some considerable degree of outdoor resting must be taking place Examinations of this sort cannot, however, tell the whole story because they omit from observation those mosquitoes that spend the whole of the gonotrophic cycle outside and probably bite outside also Search must therefore be made for mosquitoes resting outdoors, and by techniques which again are young Direct search may be amplified by the construction of artificial shelters simulating those occurring in nature, a practice developed by Gillies This technique is so far only established as applicable to a few species, but is a type which may profitably be developed for other conditions

PARASITE RATES

The parasite rate amongst infants, preferably classified in three-monthly age groups, gives more indications of immediate parasitological happenings than any other rate or combination of them Its strength lies in the fact that it gives a clear exact picture of what is happening or has recently happened Its weakness lies in the fact that it gives no picture of anything but recent happenings, for which reason it needs amplification by a study of the past history of the disease, or by a comparison of parasite rates in children and adults to show the degree of immunity developed by past experience The collection and examination of films need no special description, the possibility of making more than a guess at ages depends on local conditions but if it is needed a combination of practised judgement and observation of characteristics such as teething and walking should give a sufficiently close estimate

Whatever the findings, there should be an inquiry into past happenings and particularly into the amount of variation in malaria over the years The more objective the criteria the better Records of parasite rates taken at the same season over several years would be of most value, particularly if they were taken amongst infants or young children Changes in the spleen rate have been much used in South America for this purpose, the ratio of the highest to the lowest being considered as a measure of the "condition" or stability of malaria Inquiry will almost always elicit usable information on past variations because epidemics are always marked in people's minds, and usually in hospital and mortality records These latter were very profitably used in epidemic areas in India, the ratio of mortality in epidemic months to that in others, termed the "epidemic figure," showing the severity of seasonal outbreaks, and its coefficient of variation over several years showing the variability of t se

EFFICIE INSECTIC

Measurement of th of insec er local conditions is a necessity combinati cy and economy in control, an ore be a malaria-

survey. The effect of insecticides depends so much on qualities of wall surface and the nature of climate that results collected far away can be taken as no more than a general guide, to be refined by local trial The object of testing is to allow as many local factors as possible to come into play and testing should be carried out in houses made of local materials and substantially to local patterns The principle followed is that there should be free

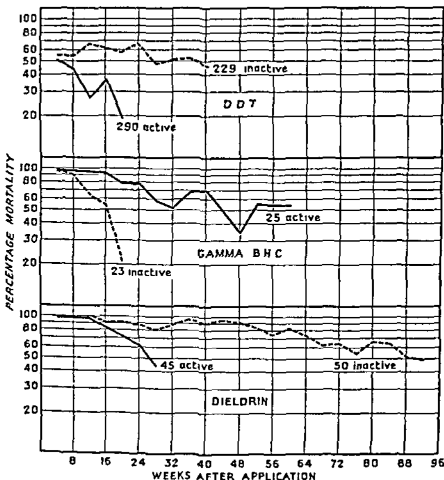


Fig 12 The anopheline mortality secured by insecticides applied in huts Two *series of results have been chosen for each of the three insecticides*, intended to contrast the persistence of efficacy on active (sorbent) and inactive mud walls The dose applied, in mgm per sq ft, is shown on each graph. Experiments were in test huts, the daily mortality amongst mosquitoes entering which are shown on the abscissæ Data, selected *for contrast and not as averages, are from records by Burnett*

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CHAPTER VIII

THE INTERPRETATION OF SURVEY DATA

THE survey provides data which can be fitted together to build up a complete epidemiological picture They come in the form of figures and the final picture is therefore numerical Expression to several significant figures gives no more than a spurious air of accuracy, but a little experience of working with this type of data will show that the methods of calculation used do not magnify errors in original observation They can be used with confidence and provided the final figures are rendered to no more than two significant figures they can be looked on as realistic

The keystone is the original determination of the probability of survival through one day, or p, and this being the case it is well to check the degree of error introduced by errors of observation of the ratio of sporozoite to total infection rates, or immediate to delayed rates It will be found that any probable degree of error leads to a very small, or indeed negligible, difference in the result because in fact a high power of p has been measured and extraction of the ninth or twelfth root has proportionately lessened any error In two surveys used as a basis for this work, the standard error of the figure has been less than 0·01

Knowing the value of p, the probability of survival through the time of the extrinsic cycle, p^n, and the expectation of life, $1/(-\log_e p)$, can be found by reference to Table 1 on p 14

The basic reproduction rate can now be tackled, either with full mathematical vigour using expression (21) given in Appendix I, or by the simple route of using Figure 13 in which much of the work has been done beforehand It gives a figure for any value of p which must be multiplied, first by the mosquito density, m, and then by the square of the biting habit, a^2, to give a basic reproduction rate The vigorous and the more craven approaches give the same results within the range of values used in the figure and the latter can be used with confidence It is to be remembered that

In either case the real curve can be compared with those in the figure and the most similar of the latter identified as giving the inoculation rate, or by interpolation an intermediate value can be estimated If the natural curve shows a material lag before rising, the main part of it can be related to one of those illustrated

The inoculation rate, estimated by calculation or roughly by the above means, represents the probability of a child receiving a successful inoculation of malaria in one day, that is, an inoculation which develops to parasitaemia One can judge the number of inoculations, successful or otherwise, which it receives by estimation of the average number of bites each day and the proportion of them which contain sporozoites, or *mas* Where malaria is mild this may be found to agree roughly with the inoculation rate estimated from the infant parasite rate, but where endemicity is extreme there will usually be a marked discrepancy, the entomologically estimated figure being even as much as 100 times higher than the parasitological one Both rates are probably nearly correct, the entomological approach has measured the total inoculations, the parasitological one the successful inoculations, which have been found to range in nature from 1 1 to 100 1

The recovery rate figures much in mathematical expressions, and an assumed value applicable to totally non-immune people is freely used in discussing the basic reproduction rate The ruling value as influenced by immune reaction can be estimated from the data provided, but in ways which are beset with pitfalls for the unwary and, because the profit to be gained is small, it is best left alone except by the mathematically inclined

Additional information can be gained from gametocyte counts in infants The earliest immune response is a reduction of gametocyte output, and in intensely malarious places it is visible by three months of age in the form of greatly reduced densities without at first marked reduction of the rate The age at which this occurs betrays clearly the load of infection under which infants live, and their response to it It constitutes the chief governing mechanism whereby transmission is stabilised at tenable levels, limiting both the infectivity of man and the infectivity of the mosquito by reduction of the ' of

sporozoites The variation in the age at which the peak of gametocytaemia is reached shows the working of the governor and the location of the balance Diminution of the load on a population results in an increase in the age at which the peak is reached, and a decrease in the discrepancy between the total and successful inoculation rates, before any other change is visible The extent of these changes following control which is only partially successful may be the only parasitological indication to the puzzled malariologist of the degree of success he has achieved If it is marked he can foresee some slight enhancement of his efficiency suddenly toppling the endemicity to nothing

Information on past history will give an indication of the stability of the disease, in places where malaria is truly stable it is very hard to distinguish between one year and the next, whilst unstable malaria fluctuates from year to year, good and bad years, epidemics and complete freedom jostle each other, with a common tendency for the worst outbreaks to recur in cycles Two direct measures have been given, the variations in the spleen rate and in mortality, but an indirect and delicate measure is available

Stability is a product of anopheline longevity, man-biting habit, and the length of the extrinsic cycle The relation to the first two is very simple, stability is directly related to the mean number of feeds on man taken by a vector anopheline during its lifetime An index of stability may be expressed in that way, or in the equivalent mathematical expression (29) in Appendix I For *A gambiae* in equatorial Africa it may be 5 or even 10, for *A culicifacies* in Madras it may be as low as 0 05, and the stability of the disease in these two places lies in these ratios one or two hundred to one Some people might prefer an index of instability or sensitivity, for which the reciprocal of the above figure is adequate, 0 1 to 0 5 in Africa and 20 in Madras

Interpretations of this type have met a very understandable scepticism from some who fear any mathematical treatment, and mainly from those who do not understand that some degree of error is acknowledged The assumptions used are not claimed as precise reflections of invariable truth but as good working generalisations of what is happening, sufficiently accurate to use

relatively small; the reproduction rate varies directly with the mean duration of infectivity, very great changes in which would be necessary to reduce the high rates common in Africa and some other places below the critical level. In the field the method has proved disappointing when used alone but may return to favour in conjunction with others.

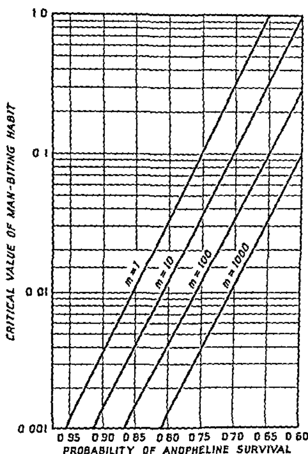


Fig 15 Critical values of the man-biting habit Each graph refers to an anopheline density shown on it.

Control by drugs has been prac d in three forms: provision
of liberal treatment facilities, ution of gam r
prophylactic drugs, and ma t of the .
Liberal treatment was for lon ne of contr
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might cure the sick, and might reduce transmission, it never succeeded in reducing it to a negligible level

The distribution of gametocidal drugs has similarly been proved a failure in most places where it has been tried, and largely owing to the administrative difficulty of securing invariable regular administration to the group which is most important—the infants

Simultaneous treatment of the entire population of an area with curative drugs has been tried many times, and recently with promising results in places where falciparum malaria predominates The object has been to secure universal cure and so to end gametocyte production and stop transmission as an adjuvant to imagicidal attack For the unaccompanied technique there is no critical level of success other than cure of all potential gametocyte carriers in the local population, for one persistent carrier could start the cycle again once the mass treatment was over Despite a promising start, therefore, the technique should be looked on as an adjuvant only, designed to expedite the disappearance of gametocytes from a population in which transmission is suspended by imagicidal attack

The policy of control will turn on many things besides the theoretical standards here described Though larvicidal measures are on the whole less effective than imagicidal attack there are circumstances in which they are to be preferred, and the choice may then depend largely on the relative ease, cost and permanence of the two The place of theory is not to lay down mechanisms for practice but in this context to show what could be hoped for from the practice of each thus making the choice easier When a method is chosen theory acts as a guide to the degree of efficiency to be demanded of it and as a background to the examination of both success and failure helping to secure economy or to remedy failure It can be trusted with good confidence to show the order and scale of control needed and so to make the rational planning of campaigns possible Survey techniques can, however, never be considered as entirely precise and so modification of technique must be foreseen

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CHAPTER X

INSECTICIDES

It is not only the nature of the substance but also the method of its use which makes the distinction between residual and immediate imagicides, and larvicides. The terminology which classifies materials as one or the other, though inaccurate, is however widely accepted and convenient and with this reservation it will be followed.

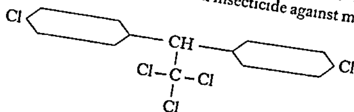
MATERIALS USED

The substances in practical use as residual imagicides in malaria control are all chlorinated hydrocarbons, having as one of their molecular components a benzene ring with one or more chlorine atoms attached. The simplest in nature, and one of the most potent, is benzene hexachloride which occurs in several isomeric forms with different spatial arrangement of the hydrogen and chlorine atoms, clearly demonstrable only in three-dimensional models. One of these, the gamma isomer (γBHC), represents about 13 per cent. of the technical product; it is a powerful insecticide and incidentally is odourless, though other isomers present in the raw chemical are less efficient insecticides and have a musty smell. The gamma isomer can be separated, but by processes which add materially to the cost of the product, and a variety of grades are in use in which it represents from 13 to over 99 per cent. of the benzene hexachloride present, the most refined being known as lindane. Careful distinction should be made between the technical product, known as BHC, and the gamma isomer, or γBHC, and dosage should always be described in terms of the latter.

γBHC differs essentially from DDT and dieldrin in that it is relatively volatile, a sufficient concentration of the vapour being maintained in the neighbourhood of crystal films to poison

mosquitoes by vapour effect Direct contact with the solid material is not necessary for lethal action which may be exerted although the insecticide is absorbed into the wall or covered by films as of smoke This volatility sets a limiting time on insecticidal action which is ended by complete vaporisation of the material The time in which this occurs depends on the dose applied on the temperature, and on the nature of the surface treated, dis appearance being delayed by some degree of absorption When present in adequate amount, and hence usually for some time after application, it kills all or a very high proportion of mosquitoes coming into contact with the treated surface Intoxication does not noticeably irritate the insect and so cause them to leave treated surfaces earlier than they otherwise would, and a fatal dose is usually picked up during the normal resting time As the available material diminishes lethal action becomes delayed and an increasing proportion of mosquitoes leave the surface in time to survive so that the mortality achieved decreases The rate of decline is probably dependent on several factors including temperature and the nature of the wall surface, but is certainly related to the original dosage Some measure of it can be seen in Figure 12 on p 111, but the amount of experimental work and especially the range of doses tested is smaller than the subject warrants There is reason to suspect that it might be rewarding to apply considerably larger doses than those so far tested on absorptive surfaces, the prolongation of effect to be expected bei probably fully in proportion to the increase in the dose applie The availability of odourless preparations now makes this feasible practice, deserving experiment more than it did at the time when smell was a limiting factor

Dichloro diphenyl trichlorethane (DDT) was the first sub stance to be widely used as a residual insecticide against mosquitoes



and is still the commonest Technical DDT contains isomers with different arrangement of the Cl atoms on the benzene rings The isomer with the arrangement shown, with the Cl atoms in the *para-para* or *p-p* position, is much more effective an insecticide than the others Routine specifications require that the percentage quantity of *p-p* isomer should be shown on *all packages of the* technical product, and it alone should be taken into account when calculating dosage DDT is virtually non-volatile and insoluble in water, it enters the insect body through the cuticle after solution in the waxy covering of the feet, it is irritant and stimulates the insect to leave treated surfaces before a fully lethal dose has been absorbed, and it enters into curious surface relations with many wall materials which result in a slow "sorption" of the insecticide

The virtual non-volatility affects insecticidal action in several ways Poisoning from an applied film is by direct contact only, and is prevented by any degree of separation, however small, whether by adsorption or sorption into the wall, by the growth of smoke films over it, or other means However, if the film remains unabsorbed and uncovered it may persist for very long periods and often until mechanically removed in cleaning or by vibration *There can therefore be no fully general statement on the duration* of efficacy of films, for it depends more on the nature of the surface to which they are applied and the treatment they receive than on the properties of DDT itself

DDT poisoning in the insect is reversible, recovery after intoxication being common if absorption ends, and intoxication is marked by irritation, the main sign of which is disturbance of rest and stimulation to flight, often ending in departure from the treated shelter It is probable that most mosquitoes are stimulated to leave the treated surface before they have actually absorbed a lethal dose and would recover if absorption were ended by their flight The continuation of absorption sufficient to kill is only ensured if the mosquito takes sufficient DDT away with it, which generally happens if the crystals are so small that some of them become entangled in the hairs of the tarsi The lethal effect of DDT films is in consequence very closely bound up with the

size of the crystals deposited, the smallest being the most lethal There is, however, some conflict here with another characteristic, sorption into wall surfaces, which inactivates the DDT and occurs most rapidly with small crystals Some compromise which secures both lethal action and persistence is desirable, and is secured if most crystals are between 10 and 30 microns in size The films deposited from oil solutions, whether continuous or as emulsions, contain crystals of a great range of dimensions, and they slowly decrease in size as time passes so that some appropriate ones exist for as long as the film remains, but wettable powders may be made up of crystals of some predominant size within or outside the useful range and so may differ very greatly in killing power

The interactions with wall surfaces are complicated In common with any other insecticide DDT may be directly absorbed into the wall if applied in solution and, unlike γBHC, is thereby inactivated Crystals deposited on the surface, whether from solutions or suspensions, may be further influenced by some materials and notably by many of the types of mud used in house construction or as internal plasters This process, known as sorption, consists in the volatilisation of material from the crystal and its deposition again immediately below the surface It is a physical effect of surface-acting forces, which varies considerably with different materials The theory that inactivation is due to chemical degradation of the insecticide under the catalytic effect of mineral salts, particularly iron salts, is now largely abandoned, and it is accepted as due to a physical process without necessary chemical change Materials differ in their sorptive capacity, some being rated in this respect as "active" and others as "inactive" Activity is related to the minute physical structure of the mud, relatively dense aggregations accompanied by very small inter-particulate spaces leading to increased capillary activity and increased sorptive activity An empirical measure of sorptive capacity described by Barlow and Hadaway relates it to sorptive capacity for other non-polar materials, carbon tetrachloride being used The soil is mixed with sufficient water to give a thick plastic mass and is pressed into cylindrical metal rings, 2 3 cm diameter

and 1 2 cm deep After drying at room temperature the rings are removed to yield small blocks of soil A block is placed in a desiccator over concentrated sulphuric acid for 24 hours and then weighed It is then placed in a desiccator over carbon tetrachloride for a further 24 hours and then reweighed The temperature of the desiccator is kept at 25° C throughout Inactive soils absorb little carbon tetrachloride, less than 10 per cent by weight, and most highly active soils absorb larger amounts—from 10 to 30 per cent—but this is not invariable The test may therefore be used to give *prima facie* evidence of sorptive capacity but should be supported by biological tests The best are those in which natural conditions are emulated as far as possible in test huts, the mortality of insects entering being estimated periodically by techniques such as described in Appendix II Large numbers of materials cannot be examined in this way, for that purpose standard mud blocks made in rings of about 12 cm diameter may be treated with DDT, stored at an appropriate temperature, and tested periodically both visually and by noting the mortality amongst mosquitoes held in contact with them for 30 minutes under a glass funnel Mortality decreases rapidly on active muds

In the field and in the test hut the influence of sorption depends on the volatility of the insecticide A non-volatile material such as DDT or dieldrin is sorbed and quickly rendered ineffective A volatile insecticide such as γBHC is sorbed but continues to act in the gaseous form, some decrease of evaporation leading to prolongation of its action The insecticidal effect of non-volatile materials is therefore reduced by activity of mud, and that of volatile ones prolonged, a contrast well displayed in Figure 12

DDT which has entered a wall surface may again move towards and on to the surface by *the process of blooming It does not* occur on mud surfaces, but is marked in some fibrous wall boards and papers which initially are very absorptive and which may regain insecticidal properties which have been latent The property has been utilised by the incorporation of insecticides in urea formaldehyde resin, the use of which is described later

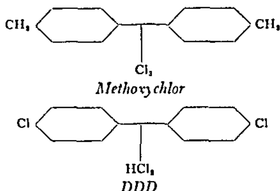
These many variable factors influencing the availability and lethal action of DDT make prediction of its effect a hazardous

affair Suspensions of wettable powders are more likely to be effective than solutions or emulsions because they are less readily absorbed, but need a check of crystal size by the sedimentation test Applied to hard non-absorbent surfaces they may be very persistent and have been successfully used as films renewed at intervals as long as 18 months and even 2 years It has been demonstrated in British Guiana that a very high, probably nearly complete, mortality is maintained for over two years in houses lined with a non-absorbent hardwood to which about 1 5 g DDT per m^2 has been applied On fibrous wall board surfaces persistence may be very prolonged On the mud plaster which is the typical wall covering of many tropical houses persistence is much decreased by sorption, though its degree may vary greatly from place to place, resulting in inactivation of a 2 g per m^2 film in a couple of months in some places and allowing continuation of action for six months or longer in others

It is probable that in such conditions the initial mortality amongst entering mosquitoes is never complete and that even good preparations do not kill more than 60 to 70 per cent, whilst poor ones may not kill more than 30 per cent of them Disappearance of the DDT depends on the nature of the surface, but before it occurs there may be some improvement in the mortality achieved by large crystal applications, presumably as a result of diminution of crystal size during sorption Owing to the relatively low initial mortality in such conditions, DDT never achieves the original potency of γBHC, and may from the start be inadequate to meet the needs of control in some highly malarious places where the vector is partly exophilic The variables are, however, so numerous and influential that any major control scheme should be accompanied by experimentation in the laboratory and in the field

Several substances related to DDT have insecticidal properties but have not achieved much prominence in malaria control The two which have been used on any material scale are methoxychlor and DDD which, though less potent against anophelines than DDT, are less toxic to vertebrates and have been used where a hazard is believed to exist, and notably in dairy-cattle sheds in

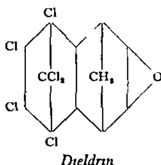
the U S A where the absorption of DDT and excretion in milk is feared



Methoxychlor

DDD

Dieldrin is one of three closely related compounds known as Dies-Alder condensation products which have marked insecticidal properties, dieldrin, aldrin and chlordane



Dieldrin

Dieldrin is the most widely used in malaria control It is a very potent insecticide, it is not volatile and apparently kills by contact only, there may, however, be a lethal effect at some distance from treated surfaces probably due to detachment of minute particles of the insecticide and such detachment may be partly dependent on climatic conditions, being more marked when the air is humid It is subject to absorption and sorption much as DDT and may be removed from surfaces in the same way It is the most toxic to man and other vertebrates of the chlorinated hydrocarbons in general use

The product of these qualities is that on hard non-absorbent surfaces dieldrin may produce a high initial mortality, approaching

100 per cent, amongst entering mosquitoes and may maintain this mortality for very long periods It has been shown experimentally to achieve over 90 per cent mortality for more than eighteen months when applied to a mud wall in which gravel was incorporated, and where the gravel doubtless gave the impenetrable background which is so helpful to the action of such products On plain mud surfaces, however, sorption may greatly lessen the period of effective action to six or even fewer months There are unexplained reversals of activity and inactivity which may be due to climatic conditions and particularly to humidity favouring the aerial dispersion of particulate matter

Neither chlordane nor aldrin are as toxic to anophelines as dieldrin and they have not come into general use for this reason They have had some vogue as alternatives to DDT to kill flies resistant to that insecticide, though the occurrence of resistance to them has largely nullified their value for this purpose, and there does not seem at present any reason to include them in the range of anti-anopheline insecticides This verdict may possibly be revoked later, they are more volatile than dieldrin and might share the advantages of volatility enjoyed by γBHC

Certain organic phosphorus compounds have come into wide use as insecticides in agriculture, but have not so far attained any position in malaria control, partly owing to their highly poisonous nature and partly owing to the ready availability of relatively non poisonous but very effective and more persistent compounds This position is however, now changing some relatively non toxic phosphorus insecticides have been produced and the development of resistance to the chlorinated hydrocarbons by anophelines will probably intensify the demand for unrelated insecticides The two most likely to secure trial are diazinon and malathion relatively non toxic compounds which have been proved effective in the control of houseflies resistant to DDT, and used either mixed with bait as stomach poisons or as wall sprays for contact action Both can be applied either in emulsions or as suspensions of wettable powders and the latter form appears to be the more effective Decomposition of diazinon is accelerated by sunlight and by heat, and such data as exist suggest that the

temperatures in some tropical countries might materially shorten its effective life Malathion is decomposed by alkalis Deposits of 180 mg diazinon per ft^2 have in one case proved effective in fly control for 49 and 47 days In another a deposit of 100 mg per ft^2 produced an initial high mortality tailing off to a 45 per cent kill in 21 days, but activity and persistence were enhanced by admixture of a synergist, piperonyl butoxide 25 mg diazinon with 100 mg piperonyl butoxide secured a 45 per cent kill at 28 days Malathion applied in parallel with the diazinon showed markedly less persistence

The adaptation of these products and other phosphorus insecticides to anopheline control is still in the very early experimental stages and not even a preliminary recommendation can be made on practice Experiment is, however, well justified

An extract of pyrethrum flowers contains four esters, pyrethrins I and II and cinerins I and II, which are acutely toxic to mosquitoes and most insects, producing rapid knock-down and death They are very unstable, being oxidised on exposure to air, and being readily hydrolysed by water Their sole field of utility in mosquito control is consequently as immediate insecticides, without residual effect, but in this field pyrethrum extract is unexcelled as a space spray The minimum effective dose, in terms of pyrethrins, is extremely low, about 10 mg pyrethrins per 28 m^3 (1,000 ft^3), which may be distributed in aerosol form in a variety of ways and from a variety of solutions It is, however, usual to distribute considerably larger quantities than this The standard spray used in simple hand operated guns was a 0 1 per cent solution of pyrethrins in oil, sprayed at the rate of 1 0 ml per m^3, while the first pressure sprayers contained 1 per cent pyrethrins, the spray being distributed at about 0 1 ml per m^3

Pyrethrum is expensive, and a number of synergists have been found which permit attainment of similar mortalities with smaller quantities The inclusion of DDT has this effect and a solution containing 3 per cent DDT and 0 4 per cent pyrethrins is equivalent to one of 1 per cent pyrethrins alone Most space sprays now contain DDT added for this purpose, but with no expectation that a residual effect will follow their use Other

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synergists include piperonyl butoxide—the most effective—sesame oil and pine oil, one or another of which are also included in most specifications of sprays

The standard formula recommended by the WHO Expert Committee on Insecticides for dispersal from aerosol bombs is one of 0 4 per cent w/w pyrethrins and 3 per cent w/w DDT to be dispersed at the rate of 10 g per 28 m^3 (1,000 ft^3) in the treatment of aircraft and ships, when high speed and efficiency of action are essential, and about one-third of this dosage, 3 3 g per 28 m^3, for routine treatment of dwellings

A number of compounds resembling pyrethrins have been synthesised, and one—allethrin—has come into commercial use as a substitute for pyrethrum extract It appears to be fully as effective as pyrethrins against the housefly, but about one-quarter as toxic to *Aedes* mosquitoes

SPECIFICATION AND CHECKING

Insecticides are the most important as well as a very expensive item in most campaigns, the success or failure of which turns largely on their quality Failure can follow, and several times has followed, the use of materials which were inadequate, either in their original formulation or by later deterioration The necessary qualities of the insecticides themselves and the materials used in formulation are now reasonably understood, and a series of specifications has been drawn up by the WHO Expert Committee on Insecticides as *Specifications for Pesticides, Insecticides, Rodenticides, Molluscicides, and Spraying and Dusting Apparatus* If small quantities only are involved it is enough if they are bought from reliable agents and accompanied by a guaranteed statement of the minimum content of active insecticide ingredient, together with an assurance that the material complies with the specifications of the WHO Manual Larger supplies should be ordered subject to their compliance with the WHO specifications and the right of the purchaser or his representative to take spot samples before consignment, arrangements being proper analysis of these samples by competent ch

The information which follows is for such expert chemical control but

reasonably carried out by the practising malariologist with simple laboratory facilities It is possible with an elementary chemical knowledge to check some points which are important and in which materials are likely to fail

In such circumstances the actual nature of the insecticide supplied must be taken for granted as precise identification is not possible Nor in such conditions is it practicable to distinguish between the various isomers of BHC or analogues of DDT Tests can, however, show with sufficient accuracy the quantity of technical DDT or BHC in a sample, and can give valuable information on particle size, wettability, suspensibility, and agglomeration after storage under tropical conditions of water dispersible powders It is not, however, possible by elementary tests to measure the quantity of dieldrin in a sample, the processes necessary being outside the capacity of the malariologist The procedures which are described in Appendix II are derived from the WHO Manual but for purposes of simplicity they have been altered in some respects, and the wording has been modified If any doubt arises, therefore, reference should be made to the original publication

DDT, methoxychlor and BHC are all hydrolysed by boiling with a solution of potassium hydroxide in ethyl alcohol with the liberation of some, not all, of the chlorine atoms from the molecules The chlorine which can be hydrolysed from DDT amounts to 10 per cent of the weight of the parent substance from methoxychlor it amounts to 10 6 per cent, and from BHC to 36 5 per cent The process requires the original extraction of the insecticide from the formulation concerned, hydrolysis of the extracted material with an alcoholic solution of potassium hydroxide, and titration of the liberated chlorine by the addition of an excess of silver nitrate followed by back-titration of the amount of remaining silver nitrate with a standard solution of potassium thiocyanate

The WHO specifications permit a maximum tolerance of 5 per cent of the nominal content, when that is 50 per cent or less, and 5 per cent of the difference between 100 per cent and the nominal content where that is over 50 per cent, in any one

sample The average of all samples from a consignment should not be below the nominal content

An approximate estimation of the quantity of pure *para para* DDT can be made by a test based on the relative insolubility of this material in contrast to its isomers in ethyl alcohol The basis of the test is the extraction of the material with hot ethyl alcohol which has been saturated when cold with known *para-para* DDT The additional *para-para* material taken up in the extract is deposited on cooling, whereas other isomers remain in solution the two can be separated by filtration and the amount of DDT in the crystalline deposit can be estimated by the hydrolysis technique The minimum *para-para* isomer content of technical DDT permitted by the WHO specifications is 70 per cent

The chief physical requirements of wettable powders are that the particles should be of a sufficiently small size, the material should be readily suspensible in water and remain in suspension and that these properties should be retained after tropical storage Tests therefore consist in exposure of the material to an artificially accelerated storage mechanism followed by sieving and suspensibility tests The techniques are virtually the same in the case of all insecticides, but they can be carried to their proper conclusion in a simple laboratory only for DDT, BHC and methoxychlor because the final estimation of dieldrin and some other insecticides is beyond the range of such a laboratory

The techniques involved are described in Appendix II WHO specifications require that not more than 2 per cent., dry weight, *of concentrate should fail to pass the sieve, and* that at least 50 per cent of active material should remain in suspension at the end of the suspensibility test, in both cases after the material has been submitted to accelerated tropical storage

Checking methods for experimental techniques may well require the estimation of the amount of insecticide applied to a wall or remaining on it some time after application Specimens may be obtained by one of three techniques test papers may be applied to the wall before treatment and subsequently removed for analysis, the insecticide on the wall surface may be removed from it by a process of solution, or a scraping may be taken of the

surface of the wall including superficial and immediately sub surface insecticide Each of these techniques has its disadvantages and its place The test paper mechanism is the most accurate means of estimating the amount applied but there is an inevitable psychological effect on the worker inducing him to ensure full treatment of the paper, which is visible to him, which may therefore not be representative of the total Solution is achieved in the material of 'Sellotape' or in silicone greases The scraping technique though reasonably accurate does not differentiate between superficial and therefore active material and insecticide which may be obscured by the wall surface and is therefore inactive

The test paper technique is self explanatory The most accurate solvent technique is that devised by Barlow using 2 inch square pieces of adhesive 'Sellotape These are pressed firmly onto the sprayed surface and the back is rubbed with a small rounded piece of wood to ensure adequate contact They are then peeled off, shaken with 20 ml of cold acetone for 30 seconds, and again extracted with three further lots of acetone In the Allessandrini method high-vacuum silicone grease is spread thinly on 2×5 cm pieces of parchment paper all excess is removed the paper is then firmly pressed onto the wall, removed with forceps, and similarly extracted with acetone Results are consistent, but the amount removed varies with the type of surface and the time since application of insecticide In the scraping technique a known area, preferably 25 cm^2, of wall surface is carefully scraped with a small knife ensuring that the entire surface is removed with a minimum of subsurface material The powder is collected and used for subsequent analysis

After evaporation the hydrolysable chlorine in such residues may be estimated by the techniques already mentioned and from it the amount of DDT or BHC probably present in them deduced Allowance must of course be made for the possible presence of chloride in the material extracted and a blank titration should be run on a sample of identical material treated in a similar way except that it is not hydrolysed The lower limit of utility of this hydrolysis test is about 5 mg of DDT or 2 mg of BHC, but no

The natural reaction of many to the suggestion of even small risks to people handling insecticides is the provision of protective clothing, but this may be poor protection and may even carry added risks In hot climates protective clothing may be a serious impediment to heat loss, and the author has personal experience of workers who have collapsed through heat exhaustion as a result of its use In cooler climates protective clothing may not be abandoned when work is finished and may merely form a carrier which keeps insecticide spilled on it in contact with the skin for long periods after work is over Masks which are often removed and left to hang by a strap may act as cups which catch insecticide to be swallowed when they are put on again A number of cases of intoxication by dieldrin have occurred in a group of workers supplied with protective clothing which, it was later discovered most of them wore not only throughout the day but also through out the night for weeks on end

For most purposes adequate protection is given to workers with DDT and BHC by the use of careful techniques which avoid the spilling or splashing of insecticide on the workers, the provision of well-kept apparatus which does not leak or spray insecticide on the handler, the prohibition of smoking at work, and the provision of sufficient supplies of soap to make washing after a spell of duty practicable Eye guards may be provided but more as a protection against the irritation of the vehicles of the insecticide than against the insecticide itself

Where more protection is required it is best given in the form of aprons protecting the more exposed part of the body and leaving ample room for ventilation while the mouth is better protected by a visor suspended from a hat or head band than by a mask which may be left off and grossly contaminated internally with insecticide in the intervals between its actual use

It is not known that any serious ill effects have occurred amongst workers applying either DDT or BHC and the simple protective measures described above have proved adequate in very wide practice There is less experience with dieldrin which has more recently come into general use, and the med[illegible] lethal dose of which to experiment[illegible] [illegible] is smaller [illegible]

other materials It is therefore for the present being used with care including the use of protective aprons and visors or, in some cases, masks In a number of campaigns the workers have been kept under very careful observation and no ill effects have been observed except in one where, as noted above, the workers kept their protective clothing for everyday and, indeed, often for everynight use Symptoms were noted after some months of occupation and were of a nervous nature, including hyper-excitability, convulsions, dizziness, loss of vision and unconsciousness Recovery followed removal from contact though in some cases it was slow As a result of this happening and despite the exacerbating conditions which preceded it special care should be given to workers handling dieldrin, including the use of appropriate and effective protective clothing which does not materially interfere with heat loss, and protection from inhalation preferably by the use of visors In all experimental work marked anorexia with consequent marked loss of weight has been an early sign of poisoning, and a watch for it should be kept amongst workers

FORMULATIONS

For residual effect an insecticide must be deposited as a film, the only practicable ways of providing the film being by the application of a liquid preparation, either a solution, an emulsion or a suspension, or by the incorporation of an insecticide in a surface material from which it blooms to the surface

There is no doubt that the application of a suspension made from one of the so called wettable powders is technically the most efficient and economic means of applying the insecticide, provided the material and the suspension are of adequate quality The initial cost, the handling and transport charges are less than with other methods, the risk of toxic effects to workers is less, and there is practically no immediate absorption of the insecticide into the wall surface as inevitably happens with oil solutions In consequence almost all campaigns and estimates are based on their use They have, however, some disadvantages chiefly in that there is inevitably some visible deposit of insecticide and vehicle on the wall which is in some degree disfiguring Though

no objection may be made to this in the typical mud-plastered house of most of the tropics, it may be a strong deterrent to acceptance in well decorated houses Emulsions consisting of a strong (30 per cent) mother solution emulsified in water are nearly free from this disadvantage, producing only slight lessening of the gloss on highly polished surfaces, and are thus much more acceptable in well decorated houses Solutions can be made which are almost entirely free of this form of disadvantage Their cost varies greatly from place to place, being relatively low in oil producing countries and high in others where they may be more than twice as expensive as suspensions Their use is therefore restricted, partly to countries where the cost of oil is negligible and in other places to houses the occupants of which are willing to carry a considerable additional cost for treatment

Emulsions involve the making of a mother solution usually in a highly reactive oil which will take up a considerable quantity, such as xylene, and the admixture of an emulsifier which is almost invariably of a proprietary nature, the best known being the American product Triton X-100 It is, however, now common practice to purchase the mother solution complete with emulsifier requiring only the addition of water Solutions can be made with kerosene, refined qualities of which will take up about 5 per cent of DDT, though this requires time, warmth and agitation Ready made proprietary solutions are now coming into more general use for this purpose and often have the advantage that they are made with oils which do not stain fabrics

There has been considerable experimentation with insecticides dissolved in varnishes and resins with the hope of getting a surface coating which is decorative or not unsightly, protective and continuously insecticidal When dissolved in resins there is a tendency for the insecticide to move slowly towards the surface so that if some is removed from it there is a fresh blooming of crystals on the surface later The most useful base found has been a urea formaldehyde resin in which insecticide up to 20 per cent of the weight of the vehicle can be incorporated, and in which the blooming process occurs The rate of blooming is greatly influenced by the final hardness of the varnish, the degree of

which must be closely controlled by accelerators or retarders It has been well established that an insecticidal film can be maintained and these products have come into extensive use for insect control particularly in kitchens and for the control of cockroaches, bugs and other pests in ships They have not, however, yet achieved any use in the field for the control of mosquitoes They are expensive, the difficulty of manufacture results in their only being available in proprietary form and they could clearly have no more than a limited use It does seem, however, that there is a small field in which that use might well be developed

Apparatus for the production of smokes containing insecticides was first introduced with the object of producing a residual film, but certainly no film of use in malaria control can be obtained in this way There have, however, been some developments of this technique to produce the immediate destruction of adult mosquitoes and as a larvicide

Smokes from so called bombs in which the insecticide is mixed with an inflammable material in a canister and ignited have very little use in this field Smokes generated by playing a continuous stream of an insecticide solution on to a hot plate in specially devised apparatus have a greater range of utility Their place lies in the immediate destruction of insects, both those indoors and those mosquitoes which normally rest outdoors and do not therefore come into contact with residual films It has not yet been necessary to resort to them for the control of exophilic malaria-carrying mosquitoes but they might well be a valuable adjunct in their control Smokes are generated in special apparatus of which the best known types are the Todd Insecticidal Fog Applicator (TIFA) and the portable Swing-Fog apparatus The smoke cloud generated is allowed to drift over the surface of the ground, and if an even distribution is to be achieved work must be carried out when the air is still, usually early in the morning With both of these types of apparatus a lethal cloud may be distributed for distances of up to 200 yards or even more, but accurate data on the dispersion of the insecticide and the amounts necessary to achieve destruction at varying distances are not available

An aerosol is a cloud containing fine droplets, the particle diameter of which lies between 0 1 and 50 microns, clouds in which the particle size is between 50 and 100 microns are termed mists, between 100 and 400 microns fine sprays, and where the droplets are larger they are termed coarse sprays Aerosols are widely used, and exclusively as immediate insecticides A refined extract of pyrethrum is almost invariably the main constituent though DDT, various synergists and particularly piperonyl butoxide may be added to enhance the effect The standard formula accepted by the WHO Committee contains a sufficient amount of refined extract of pyrethrum to give a total of 0 4 per cent of pyrethrins together with 3 per cent of technical DDT incorporated in a mixture of non-volatile oils, solvents and propellents They are normally dispersed from canisters containing a propellent and fitted with a valve so arranged that 1 g of the formulation is dispersed per second as an aerosol

STORAGE

All insecticides should be stored with care and under the coolest conditions possible Dry formulations such as dusts and wettable powders may be stored for considerable periods provided they are protected as much as possible from heat and the weather Decomposition of the insecticide is not likely to occur but there has been much trouble in the past with aggregation of particles and loss of suspensibility The present specifications are intended to ensure that this will be overcome but supplies which have been stored for any material time should invariably be submitted to the suspensibility and sievability test already referred to Emulsion concentrates are very liable to deterioration on storage, while oil solutions may be precipitated by exposure to frost

A comprehensive and excellent account of the subject is given in —

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A general appreciation of the needs of malaria control is in —

MACDONALD, G & DAVIDSON, G Dose and cycle of insecticide applications in the control of malaria 1953, *Bull Wld Hlth Org*, 2, 785–812

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CHAPTER XI

DRUGS IN MALARIA CONTROL

DRUGS have had a very variable importance in control since the time when Koch set out to prevent transmission by the wide distribution of quinine in East Africa, and this concept of control was taken up in several of the Mediterranean countries The method was abandoned as a failure but was resuscitated after the production of pamaquin and the demonstration of its specific gametocidal properties It was thought that these might give the chance of success where quinine had failed, and extensive trials were organized largely under the influence of the Malaria Commission of the League of Nations, but these again proved failures and gametocidal attack languished It may come into prominence again following the recent demonstration of the very prolonged effect, 4 weeks, of 50 mg doses of pyrimethamine in inhibiting the development of the parasite in the mosquito Drugs were widely used as prophylactics during the war, and with such success that the prophylactic approach was looked on by some as a legitimate control measure for general communities after the war ended Almost without exception programmes for the protection of the general public based exclusively on chemoprophylaxis have been abandoned, and it is now regarded as a measure for special communities such as armies and labour forces subject to special risks and under some degree of discipline, and for the individual who manages his own protection The therapeutic use of drugs is becoming more commonly adapted to the mass treatment of populations, it is valuable in epidemics, and is now looked on as possibly a great help in the first stages of malaria eradication programmes Also individual treatments are assuming more prominence as the last stage of eradication programmes, whilst anti-relapse therapy may become a valuable tool in the prevention of re-importation of the disease into areas from which it has disappeared

Unfortunately a tortuous and illogical terminology has grown up around the subject, showing more respect for the detail of past

concepts than for present knowledge or for the English language, leading to absurdities such as the restriction of the word prophylaxis (Gr *prophylaktikos*, guarding beforehand, precautionary giving use to Gr *prophylaxis*, a guarding against) to prevention by one particular route, whilst equally effective prevention by another must be known as permanent suppression, which it is not The object in administering drugs is to prevent or cure the parasitic and clinical manifestations of infection, and it may result in either success or in mere temporary suppression The words prophylaxis, prophylactic and cure will be used here in the sense of complete prevention or cure unless a partial result is indicated, while the words suppression or suppressive will be used in the sense of control of clinical and parasitic manifestations leaving a reservoir of forms from which relapse may originate This was the original intention in introducing the word suppression but by an historical quirk it has come to mean prevention of whatever degree, which is not dependent on destruction of the exo-erythrocytic forms

PROPHYLAXIS

The efficacy of a prophylactic drug, given in an appropriate regime, depends on the qualities of the drug the species the strain of parasite to which the subject is exposed and his previous experience of the disease with the consequent development possibly of a partial immunity While the qualities of drugs can be reasonably defined and largely also the responses of parasite *species*, the precise reaction of *strains* of parasite and the degree of immunity of the subject show great variations and care must be used in transferring opinions on the utility of drugs from the place where they have been formed to others where perhaps success may be more difficult of attainment In particular the results of trials made on people with previous experience of malaria should never be looked on as relevant to others without it

The major difference in this context between species of parasites turns on whether secondary exo erythrocytic forms are produced after liberation of merozoites from the first as in *Plasmodium vivax* and probably *P malariae* and *P ovale*, because this continuous production of resistant forms is a barrier to

complete prophylaxis or cure except by drugs of the 8-amino quinoline group such as pamaquin and primaquine, and perhaps by pyrimethamine The reactions of strains of parasite are unpredictable and in consequence drugs enjoy very different reputations in various parts of the world, and some account must always be taken of local experience in prescribing On the whole however, the schedules proposed have a wide application It is known that the common use of pyrimethamine and proguanil may result in the development of strains of parasite resistant to them and there is a clearly documented account of a strain of *P falciparum* resistant to mepacrine in New Guinea This resistance has, however, chiefly made itself obvious when clinical attacks were treated and has less relevance to prophylaxis which has hardly been impeded by it

Quinine, once the sole standby, is demonstrably so inferior as a prophylactic to several synthetic products that it may be disregarded Mepacrine has been proved, by intensive experiment and wide use, to be an effective prophylactic against *P falciparum* and a good suppressive against *P vivax*, but it has been nearly—and should be completely—abandoned for this purpose because toxic effects are relatively frequent Yellow discoloration of the skin may be ignored by some men though not by women Occasional severe gastro intestinal irritation when the drug is first taken is a drawback A common atypical lichenoid eruption which can amount to a widespread exfoliative dermatitis is a reason for caution, and rare mental effects, varying from euphoria to severe depression or prolonged mania, are good reasons for condemnation now that alternatives can be found

The 8 amino-quinolines, pamaquin and primaquine, have not been proposed as prophylactics on account of their toxicity

This exclusion leaves four available drugs for the purpose two of the 4 amino-quinolines, chloroquine and amodiaquine, and proguanil and pyrimethamine With only a reservation about variance in the reaction of strains of parasite, all these drugs are effective Complete prophylactics against falciparum malaria, they are effective suppressives against vivax, malariae and ovale infections and are free from important risk of toxic effect when

given in appropriate doses Chloroquine and amodiaquine are rapidly absorbed, but slowly metabolised and excreted, a sufficient plasma concentration being kept up for a week following 0 3 G of chloroquine base, or 0 4 G of amodiaquine base, to ensure their efficacy Their action is against asexual parasites on their liberation from primary exo-erythrocytic parasites Neither the latter nor secondary forms are affected Toxic effects are rare and comparatively unimportant, taking the form of headache, blurring of vision and occasional pruritus, which end on discontinuation of the drugs Neither experimental nor field experience suggests that there is any risk of stimulating drug resistance by their use

Though proguanil and pyrimethamine are distinct in their constitution, it is known that metabolism of the former gives a product closely related to pyrimethamine and active against plasmodia It is not surprising therefore that in some respects they have a close resemblance, notably in their freedom from toxicity and, unfortunately, in their tendency to stimulate the production in parasites of a resistance which may act against both Proguanil is rapidly absorbed and excreted, there is no prolonged accumulation in blood or tissues Its main action is on the primary exo-erythrocytic forms, which are apparently susceptible to it for only a brief period when 2 to 3 days old Efficient action requires daily administration of 0 1 G doses of the salt (87 mg base) with which failure of action is rare Once peripheral parasitaemia has developed, proguanil may be a very ineffective schizonticide and parasites may flourish despite its continuation, many of the known failures of prophylaxis may be due to failure to control a pre existing parasitaemia or to irregularity of administration permitting one to develop which is not later controlled There can be no sure prospect of success with smaller or more widely spaced doses, though the adjuvant effect of immunity has made twice weekly doses of 0 2 G, or even weekly doses of 0 3 G, reasonably effective in some communities with long previous experience of the disease The drug is very safe, toxic results being extremely rare after the recommended dosage and usually only occurring after gross overdosage such as 0 75 to 1 G taken

at one time, when gastro-intestinal and renal irritation follow, perhaps with haematuria, but rapidly disappear after temporary discontinuation of the drug.

It has been well established in the laboratory and in the field that the prolonged general administration of proguanil as a prophylactic may cause the selection of drug-resistant strains of parasite. The resistance is transmitted and stable but is most marked in the schizogonic stage, showing itself more as resistance to treatment of overt infection than as a failure of prophylaxis which may remain successful when treatment with the drug has become impossible. The exo-erythrocytic forms may, however, ultimately become resistant, and failure of prophylaxis may occur necessitating a change to some other drug. The similarities between proguanil and pyrimethamine are marked; there may be a cross resistance or development may quickly follow treatment with the other drug, so change should invariably be to one of the 4-amino-quinolines, which are not known to stimulate resistance.

Pyrimethamine is a simpler compound than proguanil but probably closely resembles it in mode of action. Elimination is slow and there is sufficient accumulation in the tissues to maintain prophylactic action for a week after a 25 mg. dose of the base, in which form it is prescribed. The site of action is not certain, prophylaxis may be due to destruction of merozoites liberated from primary exo-erythrocytic forms, or may at times be due to

TABLE 4—*Drugs common*

Drugs	*Prescribed as*	*Preparations available*
Chloroquine	phosphate	Aralen, Avloclor
	sulphate	Nivaquine, Resochin, Tanakan
Amodiaquine	hydrochloride (dihydrochloride dihydrate)	Camoquin, Cam-aqi, Flavoquine, Miaquin
Proguanil	hydrochloride	Paludrine, Biguanil, Chlorguanide, Chloriguane, Diguanyl, Drinupal, Guanatol Hydrochloride, Palusil Tirian

action on these forms themselves and even on the secondary forms, as is suggested by its true prophylactic effect against some strains of vivax malaria and its occasional complete cure of vivax infections It is also an excellent inhibitor of gametocyte development, and recent work suggests that this action may continue for as long as 4 weeks after one dose of 50 mg Not all strains of parasite are equally susceptible to its action, in some parts of the world it seems less effective than in others, notably in parts of Australasia and Malaysia, but in general it is a highly effective prophylactic against falciparum infections and a reliable suppressant of others, typically given in 25 mg doses once a week This dose is far below the toxic one and in proper use pyrimethamine is as safe as proguanil, but excessive dosage may cause severe anaemia This has occurred in children taking a daily instead of weekly dose of 25 mg, and acute collapse has followed the swallowing of large numbers of tablets, which are virtually tasteless and may be mistaken for sweets It has been shown in the laboratory to be a potential stimulant of resistance in the parasite, of a type probably very similar to that against proguanil, and there is now some recent evidence of its production in the field It should not, therefore, be looked on as a suitable substitute for proguanil where that drug has failed

The key to all drug prophylaxis is discipline The individual who is to protect himself can, if he will, apply it to himself and

as chemoprophylactics

Dose xpressed as	*Usual adult dose* (G) *and equivalent* (g) salt	base	*Interval between doses*	*Proportion of adult dose for children aged* Under 1	1 3	4 6	7–10	11–16
osphate	0 5 G	0 3 g	7 days	1/8	1/4	1/3	1/2	3/4
phate	0 4 G	0 3 g						
se	0 522 g	0 4 G	7 days	1/8	1/4	1/3	1/2	3/4
dro chloride	0 1 G	0 086 g	1 day	1/4	1/4	1/2	1/2	1
se	—	25 mg	7 days	1/4	1/4	1/2	1/2	1

secure virtual complete freedom from risk of malaria for an indefinite period, selecting any one of these four drugs according to its convenience, cost and appropriateness to local conditions, knowing that in some areas proguanil or pyrimethamine *may* be contra-indicated owing to parasite resistance With this reservation proguanil may often be the most suitable, the daily regime being more easily remembered and followed than a weekly one, and the low cost and low toxicity providing considerable attraction If a weekly schedule is preferred chloroquine or amodiaquine are the more universally appropriate, but pyrimethamine will in most places be equally effective, and is cheaper and even less toxic than the others

There are, on the other hand, relatively few communities in which an adequate disciplinary standard can be maintained to ensure universal and regular administration, and these few are mostly selected groups of men without attendant families It is most often reached in military or quasi-military groups, for which drug prophylaxis may be the sole sure defence when mobility prevents protection from the mosquito It is very difficult to secure the necessary discipline in a civilian labour force except in the face of some obvious peril, even then it needs an *elaborate* organisation of administrators, check-rolls and musters and, when the memory of recent risk passes, public apathy followed by opposition usually destroys it Drug prophylaxis is not therefore a practicable permanent means of protection for such groups and ought to be regarded as a temporary measure, easily and quickly applied, which gives relief from an immediate emergency and time in which to institute other and more reliable procedures The discipline of groups is applied from without, in the form of musters or parades, which makes weekly administration more *economic* than daily Proguanil is then often the least appropriate, pyrimethamine the most economical and in most places fully effective, while chloroquine or amodiaquine are universally effective

MASS TREATMENT

There is as yet too little experience with the association of mass treatment and imagicidal attack to lay down any definite

procedures for general use, it being only possible to indicate what experience has so far shown There has been experimentation in the subject by Farinaud and Choumara in a truly hyperendemic part of Indo-China In all cases imagicidal control was practised but where this was not associated with drugs it was found, as is usual, that it was many years before the parasite rate became negligible After some discouraging experiments with continuous mepacrine, courses of continuous chloroquine were tried and gave hopeful results but were abandoned owing to the impracticability of the general adoption of continuous medication Brief courses of general therapy with a variety of drugs and in association with the imagicidal attack were then tried Chloroquine, given weekly for 2 months in a dose of 0 6 G for adults, produced a reduction of the parasite rate which was sustained for 10 months after the end of the course, indicating that the majority of the infections had been cured Pyrimethamine in a dose of 50 mg for adults and 25 mg for children over 4 years of age gave disappointing results In each of three experiments there was a dramatic reduction of the parasite rate which, however, rose rapidly after the end of medication to reach its former height, indicating that few of the infections had been fully cured Amodiaquine given fortnightly in a dose of 0 6 G to adults and children over 10 with smaller doses to younger children for a period of approximately 6 months, gave very encouraging results with remarkable and sustained reduction of the parasite rate These authors concluded that a mass treatment limited to 2 or 3 months and consisting of 5–7 doses of amodiaquine to each individual would be the most appropriate for combination with imagicidal attack Vincke, working in the Belgian Congo, used pyrimethamine in doses of 25 mg for those over 4 years of age and 12 5 mg for those under, once a week to the entire population for periods varying from 5 to 21 weeks All the schedules which he used resulted in remarkable diminution of the parasite rate and the maintenance of this reduction for 6 or more months after discontinuation of the drug, indicating that cure had been obtained in the great majority His original work was amongst immigrants to a non-malarious area who could be followed for a long period with some

available concerning two, the Chesson and Korean strains The former, which is of a tropical type with a regular relapse pattern, *is very resistant to treatment*, while the latter, which is of a temperate type with a marked tendency to lie dormant for long periods, is more amenable to treatment.

When given during the late clinical phase of the disease and in association with a schizonticidal drug 20 mg of primaquine for 14 days reduced the relapse rate of the Chesson strain from 100 to 15 per cent, and 10 mg reduced it to 65 per cent In the case of the Korean strain of vivax malaria 15 mg for 14 days gave a radical cure in all of 348 cases, whereas the relapse rate in those treated with chloroquine alone was 39 per cent Given *without* a schizonticidal drug during the period of latency primaquine has a comparable effect, 15 mg for 14 days producing a radical cure in the great majority of those infected with the Korean strain

Primaquine has been used to prevent relapses in immigrants into a cleared zone from an infected one, but only so far under military conditions United States forces returning from Korea have been given a routine treatment of 15 mg of primaquine for 14 days without special medical supervision on board their troopships Application of this technique to civilian practice has yet to be developed but is almost inevitable There have been examples of the reintroduction of the disease into cleared areas by migrants, as in French Guiana by labourers migrating from the Antilles It does not seem either necessary or desirable that individual travellers should be subjected to routine anti-relapse therapy but there is little doubt that there will arise a need for the treatment of groups of people on some such mechanism as that used in the case of the U S troops Treatment will probably consist of a single administration of 0 6 G of the base of either chloroquine or amodiaquine Where the risk is thought to lie in the importation of *P vivax* immediate treatment with chloroquine will probably be combined with a 14-day course of 15 mg of primaquine, the recipients being inspected medically half-way through the course People may however be rendered temporarily harmless, or non-infective to mosquitoes, by administration of a

single dose of 0 6 G. chloroquine base with 50 mg of pyrimethamine, a rationale which deserves trial and which may be developed in the protection of areas from which malaria has been eradicated

There is an excellent comprehensive account of anti-malarial drugs, with a good bibliography, in —

COVELL, G, COATNEY, G R, FIELD, J W & JASWANT SINGH *Chemotherapy of malaria* W H O Monograph Series No 27 Geneva, 1955

Special aspects of their use as supplements to imagicidal control programmes are recorded in —

FARINAUD, M E & CHOUMARA, R La prophylaxie du paludisme dans pays montagnards du Sud Viet Nam 1954, *Bull Wld Hlth Org*, 11, 793–838

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CHAPTER XII

THE CONTROL PROGRAMME

A MALARIA control programme turns first on an original appreciation of the incidence and distribution of malaria, its stability and season, the vector and its habits, such as described when discussing survey procedures From this appreciation decisions on policy must be made on the degree of control to be aimed at and the mechanism to be used Fortunately the once widespread idea that there was something harmful in the control of hyperendemic malaria has been killed and questions of policy now turn on the areas where control is to be practised and whether the objective is a limited one or that of complete eradication This nowadays should largely depend on whether the organisation undertaking control is a national one interested in the welfare of the country as a whole, when ultimate eradication seems a generally logical end to work towards, or is a local one concerned only in a small area from which eradication would be fruitless owing to constant reintroduction If eradication is to be attempted there may be, in some few places, questions of whether it should be through total eradication of the mosquito, or through its prolonged control until the parasite is eliminated In the present state of knowledge and ability vector eradication is not a general possibility and would only be practised in places where there is a physical barrier to reintroduction of mosquitoes, or where the insect has been demonstrated as readily susceptible to eradication There are for instance island territories in the Caribbean and elsewhere where mosquito eradication might well be a more logical aim than control, and it might be attempted by imagicidal means in places infested by *A darlingi* and perhaps *A funestus* The possibility of malaria eradication makes it desirable to think of control schemes in terms of natural areas which can be to some extent isolated from other malarious zones, and to attempt integration of control in such areas even though they extend over political frontiers and international co-operation is necessary

Following decisions on these points come those on the choice of mechanism, very largely a choice between imagicidal and larvicidal techniques and for nearly all places ending in a decision for the former There are, however, a few places where a decision to rely on larvicidal techniques may be justifiable, those in which breeding of the vector species is confined to readily defined limited water areas which are relatively few in number in contrast to the houses they influence There are many towns where this is the case and there are other special cases where swamp breeding mosquitoes can be handled more logically by swamp drainage than by insecticidal application to houses There are others coming under the head of man-made malaria where the object should be to eliminate the fault rather than to meet its results by measures causing inconvenience to the householder and expense to the medical department, neither of which is responsible for the nuisance However, on analysis imagicidal control will be found preferable in the vast majority of places It is the only technique by which it has proved possible to control malaria over entire countrysides, rural and urban, and the circumstances in which it cannot be used to achieve this end are certainly very few if they exist at all No large project should turn from it to other mechanisms without very serious justification

Both imagicidal and larvicidal mechanisms demand their own systems of checking to ensure efficiency, and they are described in relation to them Whichever is used there is also a need for assessment of the effect on malaria Spleen and parasite rates taken on school children and older groups are very unreliable, almost useless, guides to short term changes in incidence and particularly to rapid reductions in incidence Hospital statistics are indicative but no more, for experience shows that the diagnosis of malaria continues to be made long after the disease has disappeared There is only one reliable indicator, infants, and especially infants born after the control programme has been started, who should remain universally and consistently free from parasites if effective control is being practised Systematic surveys of infants are therefore needed and by whatever process may be most applicable to the country, in many the routine collection of

blood films in infant clinics may be the most appropriate but the existence of areas not normally served by them should not be overlooked High standards of examination and diagnosis of films must be maintained, and this may be difficult in busy clinics without special staff once malaria becomes looked on as unimportant Usually this need will lead to the provision of special facilities and staff for examination of films, under the supervision of the malaria service

Routine collection of blood films from the general population will, however, again become important when it is agreed that malarial endemicity has died down and search is made for residual foci and recrudescences of the disease, and it will make the provision of special facilities more important In this case films will probably be taken in hospitals and clinics, and will be required of all practitioners when clinical malaria is diagnosed, and since in the vast majority of cases the result can be of little advantage to the practitioner or the individual patient it would only be possible through a service designed for the purpose

THE IMAGICIDAL PROGRAMME

On a decision to undertake residual spraying a further appreciation is necessary, of the resting places of the vector anopheline to determine the needs for treatment of sleeping rooms, other rooms, animal shelters or other places, on the efficacy of insecticides against them under local conditions and particularly on local wall materials, on the susceptibility of the anopheline as a check on any later suspicion of resistance, and on matters such as the typical formation of houses, the areas of wall surfaces to be treated and the means of transport which are appropriate For any really large scheme it is most desirable that a test hut mechanism should be established so that factual comparisons can be made of the efficacy of insecticides under true local conditions, and much risk of either waste or inefficient work thereby avoided

The choice of insecticide should properly be controlled by an experimental technique of this sort, and will often turn on questions of relative cost, including materials, long-distance freight, local transport with labour and other application charges,

which will be different for each of the available products The two which can be relied upon to produce a really high anopheline mortality in almost any circumstances are γBHC and dieldrin, and in places where the malaria is stable and carried by an anthropophilic and long-lived anopheline the choice will often lie between them γBHC will usually be preferred where the transmission season is short, of the order of three months or less It will rarely be found appropriate to apply less than 20 mg of the gamma isomer per square foot, and present *indications* are that larger doses of 40 mg or even more may prove valuable and practicable if the odourless lindane product is used Where the season is longer questions of cost will determine the choice between repeated applications of γBHC and more widely separated doses of dieldrin With a six-monthly spraying schedule an initial dose of 50 to 75 mg followed by later applications of 30 to 50 mg per ft^2 of dieldrin will often be found appropriate, though local experimentation may suggest considerably different intervals and doses When dealing with mosquitoes which are normally zoophilic or in other ways somewhat inferior vectors a cost estimation may show that DDT is the more economical material and it is likely to be effective, and in many places a dose of 200 mg per ft^2 will be found appropriate on a six-month cycle In some places and notably in parts of Central America local conditions may make this dose effective for much longer periods, but this can only be determined by local experiment

In almost all cases the most effective formulation will be a suspension in water of a wettable powder, the demand for other formulations arising from the disfigurement produced in well decorated houses by its use There may therefore be need for emulsions or solutions replacing a small part of the suspension, and often charges are levied against householders who elect to have the more expensive product

The essence of an organisation is the spraying gang, the size of which will often be determined by communications and transport facilities In any large scheme it will be carried with its apparatus and supplies in transport, usually a truck but at times in a special vehicle, by boat, or by animal transport Economy usually

requires the formation of the largest gang which can be conveniently carried with its materials in the appropriate unit of transport, and it will often prove to consist of a foreman, a driver, 4 to 6 sprayers with 1 to 2 reliefs who will service the sprayers and exchange duties with them The first step in organisation is the determination of the size of the gang which is appropriate and of the number of houses which can be treated by it in the course of one spraying cycle The size of houses, the numbers of rooms and the ease of communication have much bearing on this and local experiment with a pilot team is essential, it will often be found that a gang of the size indicated can treat 1,000 small houses a month and 6,000 in a six-month cycle of work, protecting perhaps 30,000 people

A pilot gang, carefully supervised, can convert original estimates into firm figures on the basis of which the proper size of areas of operation can be worked out and they can be marked out on maps and on the ground The pilot area can then be used as a training ground, further gangs trained in it can be allocated to others and rapid expansion can thus be achieved

Within the gang it will be the duty of the foreman to ensure that a regular schedule is kept, that villagers are informed beforehand of the arrival of the gang and the necessary preparations made in the way of opening houses, covering foodstuffs, and removing bulky furniture from walls, the foreman will supervise spraying and record the treatment of each house both in a ledger and in the house itself, where a statement of the next due date is also welcome These foremen in their turn need help and supervision from a local centre of control, supplies and records, which may be capable of handling half a dozen gangs and will need a higher grade of supervisory staff, with transport, store and office accommodation

The control to be exercised over work is of two types, disciplinary and technical The former, ensuring that spraying is carried out as directed, requires that a firm schedule of work should be prepared beforehand, the immediate reporting of any deviation from it, and an inspection system by supervisory staff Technical supervision is concerned with the qualities of the

insecticide supplied, normally handled at a central unit and referred to later, the rates of application to walls, the duration of efficacy, and effect of the insecticide on anophelines Such supervision should normally be undertaken by the local control centre, dispatching material to a central laboratory as might be necessary

Control of application rates by test papers applied to the wall beforehand is a good check on technique for the information of workers but a poor one for control in that the test area is visible to the worker at the time of application Wherever possible random checks should be made on walls treated recently and using either the techniques of separation of insecticide from the wall by 'Sellotape' or silicone grease or by scraping the wall surface, the material being then submitted to chemical analysis When DDT is used it may be possible to arrange that the Allessandrini test, or a similar one, is carried out in the local centre

The absence of anophelines in treated houses is a poor check on efficiency and not to be relied upon Their presence, however, may be important as an indication of failure of action or of insect resistance, and some searches should be made The prevalence of anophelines in untreated shelters and of their larvae in breeding places may, however, prove valuable guides to what is happening and an effort should be made to record them from the first so that changes can be noted Age classification of adults found in untreated houses, using the ampulla measurement technique, is a valuable guide to the degree of mortality being achieved locally and though it demands techniques only possible to the entomologist it should be carried out wherever possible Routine susceptibility tests are also necessary, carried out periodically and also if there is any suggestion of possible resistance in the form of undue anopheline prevalence or of an age constitution consistent with survival in the face of treatment

The point in examining breeding places is to note whether any great decrease in the breeding of the vector species has occurred, it would be an indication of early progress towards eradication of the anopheline and if found should lead to a reconsideration of the scheme to see if it might be modified to complete the process The necessary data are therefore some numerical statement of

larval prevalence at the start of the scheme with periodic reassessment at the same places and under similar conditions It should not, however, constitute any major part of the work of the control group

The scale of provision of gangs and local centres will depend on the size of the area to be controlled, but whatever it is they need control by a central organisation the quality of which will reflect that of the director who needs considerable knowledge of malariology, administrative ability, powers of leadership and versatility. The functions of the centre are advice to the government on policy formation, tactical management of control, maintenance of office and records, and the purchase, checking, handling and distribution of stores, staff training and management, and technical supervision Many of the necessary provisions are common to other administrative units, but a large scheme requires a laboratory with chemical, entomological and parasitological sections each under a competent head The chemical section should be responsible for the control of specifications of materials, largely according to the *Specifications for Pesticides* by WHO, and for the management of chemical testing of work in the field The entomological section would be largely concerned with original survey and later systematic appraisal of entomological results, including the biological testing of insecticides, the susceptibility of insects to them and the happenings to anophelines under control The parasitological section would grow in importance if the scheme proceeded from control to eradication, blood films needing examination at all times, at first largely from infant groups and later from expanding sections of the hospital and general population

The invaluable and irreplaceable training is in the field, the strongest emphasis being on it with only subsidiary concern in systematic instruction The virtue of residual insecticides lies to no small extent in that they are applicable by a technique which can be taught as a drill requiring the minimum of judgement by the field staff The first gang must be trained direct by the professional staff and kept under the closest supervision until a successful technique is established Ideally this initial gang

should continue as a training gang, new staff working with and alongside it until the techniques are mastered, and certainly all new foremen and junior controlling staff should serve a term with such a pilot team Beyond this, sprayers and similar staff need sufficient instruction in what they are doing to stimulate their interest, and if possible their enthusiasm, but there is little point in pushing instruction past this stage It is equally important that the junior controlling staff should be drilled systematically in a few techniques, all carefully standardised, and that they should not be confused by discursive courses presenting many alternatives of action Some of this instruction might be given at the central laboratory, but it should certainly be pursued as a practical exercise in the field under the direction of previously trained people of similar grades There will also be a need for the training of laboratory technicians at the base in standard procedures For professional staff with basic professional education the best training is also on the job Originally this may not be possible locally and the value of visits to schemes in other countries, in which the visitor participates for a time in the work of his professional colleagues, cannot then be over-estimated Didactic courses of instruction are at times valuable but must be looked on more as providing an educational groundwork than as a detailed training for a particular post

THE LARVICIDAL PROGRAMME

The place of larvicidal work, or more correctly the prevention of anopheline breeding, is distinctly limited and it should not be undertaken except for special and definable reasons Where it is appropriate the object is to control all breeding within some defined area, often described in terms of a radius around an inhabited place An enlargement of the original appreciation is needed for larvicidal control, an exact incrimination of the vector with exclusion of other species from suspicion, which requires a considerable programme of mosquito collection and dissection, a precise study of the breeding places of the vector, leading to an incrimination of a type of water in which it may be found breeding, an analysis of the frequency of this type of water, and

information on the normal range of flight of the vector from its breeding places

On this appreciation a programme can be built It will include first a decision as to whether the vector species only is to be attacked or mosquitoes in general The first is indicated where the incriminated type of water is limited and definable, readily recognised by subordinate staff, and where no nuisance or other mosquito-borne diseases call for control of other species In the range of anophelines with highly specialised breeding habits such as *A maculatus*, *A minimus*, *A fluviatilis*, *A superpictus*, and *A bellator*, a strict species sanitation may be aimed at, but where breeding is commonly widespread, as with *A culicifacies*, *A gambiae*, *A funestus*, the *A maculipennis* complex, *A darlingi* and others, a campaign approaching general mosquito control may be inevitable

After this a decision must be made on the radius of control needed around places to be protected, often of the order of three-quarters of a mile but extending well beyond this where breeding is profuse or the vector is a good flier, as is the maculipennis group Within the chosen radius all waters of the incriminated type should be controlled, and this regardless of any finding that a particular stretch is found free from larvae on any particular occasion Methods of search are primitive, much is overlooked, and negative searches do not justify inaction, though if consistent they may justify a review of the original incrimination of that type of water

The mechanisms of control may be chemical, biological or mechanical, and all must be looked on as temporary measures demanding periodic action though the intervals may vary Chemical control can be immediately effective and will be the usual starting point The choice of larvicide is now relatively easy, a solution of DDT in oil, either as such or emulsified in water, having great advantages over most others There is no particular reason to think that larvicidal use is more likely to cause resistance than is imagicidal, since the once widespread hypothesis was founded on circumstantial evidence which has not increased with time, and there is no reason to avoid DDT on this account.

The effective dose is about 0 1 lb DDT to each acre of water surface, which is provided by 1 6 pints of a 5 per cent solution, one gallon of a 1 per cent, or 10 gallons of a 0 1 per cent emulsion, in which last form it is usually applied In anopheline breeding places residual action is not to be expected, the DDT being quickly precipitated in colloidal aggregates with other material commonly present in the water, and fresh applications must be made throughout the transmission season and at intervals not exceeding the minimum time of development from egg to pupa, usually weekly Preparations of γBHC and dieldrin have been advocated but do not seem to have material advantages over DDT, and in one case the pellet form of dieldrin larvicide has been found to exert a local larvicidal action near the bottom of the water, destroying anophelines only when it is shallow and perhaps even favouring them when it is deep by destruction of competitors and natural enemies

Biological means of control are too numerous and too localised in their application to give in detail Their principle is that they act by modifying the condition of the water so that it becomes unsuitable for the vector species, without actually eliminating the water All types of herbage control which lead to mosquito control come under this heading They are very numerous and of very extensive application, but their utility is limited to particular anopheline species and the techniques can only be derived from a detailed knowledge of the breeding requirements of the relevant species They were very largely used for instance by the Tennessee Valley Authority for the control of *A quadrimaculatus*, shore-line vegetation being controlled by oscillation of water levels and to a lesser extent by herbicides Another accepted and still valuable technique is the control of salinity in places where vectors, such as *A melas* and *A sundaicus*, favour brackish water, and another the preservation of shade over the breeding places of mosquitoes choosing sunlit waters, such as *A maculatus* and *A minimus* Each of these has once had a large place, but it is now to be remembered that they are in competition with an imagicidal control which can be perfect, and they should not be pursued to its exclusion unless they can match it in results

Mechanical control is by elimination of the breeding place, and typically by drainage Many types may be applicable, but some have been developed in relation to the control of particular anopheline species The practice of subsoil and contour drainage in Malaya was developed for the control of *A maculatus* and has been modified from normal agricultural practice in the process The time has, however, passed when it was the function of the malariologist to devise drainage mechanisms and to carry them into practice, these should now be the concern of the engineer working in collaboration with the malariologist, who should supply the necessary specifications for the work that is to be undertaken according to the object in view

As with any other mechanism, larvicidal practice needs disciplinary and technical control Disciplinary control of any periodic process such as the application of a larvicide requires standard schedules of work and inspection, usually taking the form of examination for larvae on the day after larvicide is said to have been applied Technical control mainly centres on verification that the correct type of water has been incriminated and that all foci of it have been identified and treated, and to avoid repetition of previous errors a different approach must be made This is best in the form of searches for adult mosquitoes the careful recording and mapping of all positive catches, and a watch for foci in which they continue despite control Existence of such a focus is to be taken as proof of continued breeding and met first by a check on standard procedures and if that is fruitless by a fresh search for previously undetected breeding places In this way larval work can be refined until it is perfect, to the stage of local eradication of the species concerned

Organization is again based on the peripheral workers—the sprayers They usually work in gangs of two and a pilot scheme shows the amount of water which one such gang can effectively cover in five days' work, leaving one day for overhaul of equipment and remedy of omissions and one for leave A series of zones are then mapped, each equivalent to one week's work, and a gang appointed to each A number of zones, perhaps half a dozen, are grouped into a district under a local controller who has local

charge of stores and records and has under him a couple of collectors who can undertake the larval and adult searching needed in supervision The districts are grouped into larger units and so on until a complete manageable pyramid is built up Central technical control requires a director with the services of an entomologist and a parasitological laboratory where measures analogous to those usual in imagicidal programmes are undertaken

Present larvicidal programmes do not often extend over great areas, and require only a section of this organisation, branched off from the more widespread imagicidal scheme and coming under its general control

THE CHEMO THERAPEUTIC PROGRAMME

Control in normal civilian conditions is very rarely attempted by means of drugs alone, but they may have some place in association with schemes of mosquito control and especially with those leading to eradication of malaria There is the greatest likelihood of value from them when *P falciparum* greatly predominates over other species of parasite, when they might be widely used with the rational objective of securing an early diminution of the reservoir In some past schemes they have been given to a limited part of the population believed to be most at risk and to constitute the greatest reservoir—infants and children—and administration has been by nurses in clinics, and in schools It is, however, well established that this does not reach the entire reservoir and though the limited approach is a valuable aid it could be improved upon by making it more general, and in that case it might be carried out for a much shorter period

Experimental work has been carried out showing promise in this general treatment, and it is described elsewhere in the section on drugs in control There is, however, no background of experience on which to build a scheme of general administration, even for a short time, and it would have to be worked out in relation to local conditions and subject to pilot test in limited areas

The more prolonged administration of drugs to a more limited group has often been practised, and is based on utilisation of

existing agencies such as schools and clinics It formed a material element in the successful control of malaria in Madagascar, weekly doses of chloroquine being given to all under school leaving age Chloroquine has principally been used but the indications are that amodiaquine might be equally effective, and that in some places pyrimethamine might be substituted

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CHAPTER XIII

THE ERADICATION OF MALARIA AND OF MOSQUITOES

MALARIA ERADICATION

THE concept of eradication of malaria arises from experience, partly of natural happenings in northern Europe and America, and particularly from the effects of continued and fully effective control in places such as Crete and the U S A It is to be clearly distinguished from both malaria control and vector eradication Malaria eradication means the ending of the transmission of malaria and of the reservoir of infective cases in a campaign limited in time and carried to such a degree of perfection that when it comes to an end there is no resumption of transmission Malaria control implies the reduction of the disease to a prevalence where it is no longer a serious public health problem, carrying the implication that the programme of work will be unending, maintaining control by continuous active work Vector eradication means the total eradication of all members of the vector species concerned so that they do not breed when the campaign against them is ended Vector eradication is an attractive idea, and has been achieved in a few places, notably some infested by *A darlingi* and *A funestus*, *but it is not so generally attainable that it can be* recognised as an objective except in special circumstances Malaria eradication appears, however, to be widely attainable and by mechanisms which are within the technical and financial reach of most countries, though not yet perhaps of several African ones The process requires a temporary increase of expenditure above that of a control programme at the time when both vector control and surveillance overlap, but this is followed by a time of decreased expenditure when insecticidal work is abandoned progressively from one place to another It does imply the application of very high standards of technical and administrative control to ensure that fully effective work is carried out throughout even the most remote parts of the area in which

transmission takes place It also requires a clarification of ideas keeping the concept of eradication constantly in mind often at the expense of by-products of control such as the reduction of nuisance mosquitoes and the management of other insects of medical or social importance The stimulus which has brought the concept into prominence is the appearance of strains of anophelines which are resistant to the chlorinated hydrocarbon insecticides and the fear that long-continued control based on their use might break down The subject has been considered by the Eighth and Ninth World Health Assemblies, which have recommended that eradication should be assumed as an objective in all malarious parts of the world except equatorial Africa That region was excluded because the past history of control is not such as to give confidence that the object is attainable The recommendation has been examined and accepted by the various regional organisations of WHO and it seems possible that the obstacles to eradication may soon be overcome in many African countries

A malaria eradication programme includes an administrative machine managing two main components, a vector control programme which is attempting to stop transmission and a surveillance mechanism attempting to measure the diminution of the reservoir of infective cases, to recognise its disappearance and find any introduced or recrudescent foci Efficient vector control brings transmission rapidly to an end, but there remain within the population infective people who may from time to time have gametocytes in their blood, and from whom a recrudescence of the disease could start if control measures were abandoned If, however, the control is carried on for a sufficient length of time the number of possibly infective persons steadily diminishes and within about three years almost all would be cured, either by natural or artificial means Eradication could therefore be achieved by a sufficiently thorough and all-embracing campaign carried on for a sufficient length of time It is probable that transmission would not end simultaneously in all parts of the countryside, being continued longer in some than in others, so that for the latter part of a prolonged scheme there would

probably be small areas of transmission in the general area where it had been brought to an end Eradication could therefore be expedited if an active search were made for infective individuals and particularly for residual foci of transmission Therefore universal insecticide application is first practised alone, it is then accompanied by a deliberate case-finding mechanism, and finally abandoned to give way to a case-finding mechanism and emergency arrangements to deal with any foci which may be found Eradication may justifiably be claimed if an active case-finding campaign has been carried out and no primary indigenous case has occurred in the region for 3 years Even after this period infections might reappear either owing to reintroduction of the disease or to late relapse of cases, so that it is necessary to make the disease notifiable and to treat it when it occurs as highly infectious

The eradication campaigns which have been so far carried out have been based on an original insecticidal campaign which has been continued for sufficient time for the great majority of infected persons to recover by natural processes, and periods of from 3 to 5 years' continuation are looked on as normal It would, however, clearly be advantageous to hasten the cure of infective people by artificial means, and there is reason to think that the preliminary phase could be completed within a year or so if this could be done Recent experimental work with pyrimethamine, amodiaquine and chloroquine indicates that they can be effectively used in the mass treatment of the entire population to ensure the radical cure of a high proportion of falciparum cases There has been some original experimental combination of such mass treatment with general insecticide application, which is fully described in Chapter XI, and there is considerable promise in this combined method of attack though great administrative difficulties would be involved and would have to be tackled by, amongst other things, careful education of the public

The mechanism of case-finding and clearing up of residual foci must depend very much on local circumstances and will vary greatly from one place to another The objective is to find all possible cases of malaria, to render them non infectious, and also to follow the history of infected people, to identify the place in

which they became infected, and to bring any continuing transmission there to an end As a necessary preliminary malaria must be made notifiable A central organisation takes up the examination and subsequent treatment of all notified cases, combining with it a very active search for other cases, using all means at its disposal, and particularly such measures as the taking of blood films from all cases with pyrexia attending out-patient departments or dispensaries A very considerable diagnostic service combined with a field mechanism is therefore necessary As the programme continues large numbers of blood films must be examined though the proportion found to be positive progressively decreases Whenever a positive film is found arrangements are made to see, treat and make inquiries of the person from whom it came and to trace if possible the probable place of infection Further work is then undertaken in this place, involving the taking of blood films from people living in it, treatment of those people found positive, inquiry into the insecticidal history of the area, and a study of anopheline prevalence with, if necessary, the re-institution of insecticidal treatment When this process starts cases may seem to occur in a more or less random manner over the countryside, but when it has been continued for some time it may become possible to recognise the circumstances in which residual foci may be expected, and a more active search can then be made for such places without necessarily the lead of an initial case Recent experience shows that the objective can be obtained with greater ease than was previously thought and that there is less danger than previously expected from persons relapsing a long time after their original infection Recrudescences in places where eradication has been claimed have been very few and have been noted before they gave rise to any material epidemic conditions

Malaria eradication schemes must necessarily be large and are typically carried out on a national scale, and it may prove desirable that they should sometimes be carried out through geographical areas which might extend over the frontiers of more than one country The first step is the formation of a plan dealing with the feasibility of the scheme, its extent, the nature of the programme, and costs, in the preparation of which the Sixth Report of the

WHO Expert Committee on Malaria should be consulted This plan should then be accepted by Government, to which it should be presented as a whole and not as one to be reconsidered from year to year, and in presentation it should be emphasised that any interruption in the campaign might result in the loss of ground already gained and thereby cause considerable waste The programme should include the setting up, if it does not already exist, of a separate division of the Department of Public Health dealing exclusively with the malaria eradication scheme, to which funds would be separately allotted, and which would need support by budgetary provision made in advance for several years There should be a legislative background dealing amongst other things with the scope of the scheme and the functions of the division, the control of funds—considerable discretion in detailed allotment being left to the director—rights of entry to and treatment of premises, notification of cases and submission of blood films from pyrexial cases, and the right to require treatment of individuals found to harbour malaria parasites The need to exercise some of these rights might not arise until the scheme was well advanced, and the law should be framed so that various sections could be brought into force by regulation at appropriate times

Within the division there should be a complete integration of administrative ability, professional skill, and routine working—all of a high quality Sound administration is an absolute necessity and the malariologist must either learn and adapt himself to administration or agree to work under one specialised in that art Though essential, it should not become the centre point of the scheme, and should keep its place as an auxiliary established to meet the needs of the other services, placing staff materials and equipment where they are needed at the right time, and ensuring co ordination of work in different areas The entire scheme should be under close central control, but with decentralised executive work The central organisation would necessarily be controlled by a director operating several sections dealing with epidemiology and entomology, administration of staff, insecticides and their chemical control, accounts, stores and records, and research and training In most places many of these could be

built up from existing materials, and it is very desirable that research and training should, if possible, be incorporated in the form of an existing institution, such as a Malaria Institute, which is made a part of the organisation For executive purposes the whole area would be divided into regions, each under the control of a regional field director, who should be a man with considerable epidemiological knowledge and understanding of the problems involved so that, whilst carrying out the directives of the central organisation he could *meet and deal with day to day problems* whether epidemiological or administrative, as they arise Within this regional organisation the working unit is a spraying gang half a dozen of which come under an inspector who is the key man in routine working and who is responsible for day to day supervision High standards are needed at this level, and it is essential that the inspector should be carefully chosen for his full understanding of the work of the operatives and the difficulties in their path If possible, inspectors should be created by promotion of people who have actually been employed in the spraying process and in recruitment it should be ensured that some people of a calibre suitable for promotion are taken on to spraying gangs *In later stages of the programme spraying gives* way to surveillance as the main regional activity, and the inspector then controls the taking and despatch of blood films as he had previously been in charge of spraying

As a background to this a considerable training programme is necessary, and as much of the training as possible should be done on the job For this purpose an original pilot zone should be operated, at first under the immediate direction of the superior professional staff and later passed over to normal regional staff The first objective in this pilot zone would be to establish standards of work, both in terms of quality and quantity, determining the normal size of task for each group of people, the number of houses which can be sprayed by one gang, and such like matters Once these standards have been fully established and the technical quality of the processes has been proven, this pilot zone may be continued as the main training area to which new staff are allotted before being dispatched to the areas in which they are to work

Comparable training arrangements will be necessary in the laboratory, dealing with such matters as the collection and dispatch of blood films, of mosquitoes, the recognition of anophelines of the area, the examination of blood films, the maintenance of equipment, the keeping of records and the movement and control of stores The general principle should be that a man goes through a course of training in one of these subjects at a time and is then posted to his job A man who shows promise should be brought back for short periods of instruction in other functions, and thereby enabled to acquire one by one all the techniques involved in the scheme and graduate for promotion This type of training is much more appropriate and adapted to the needs of a mass campaign than discursive training covering at one time a variety of subjects

The spraying programme involved in an eradication campaign is of the normal form and needs no special description except in relation to its administration, which must be arranged to secure universal application and the universal attainment of a high quality of work. Firstly, the work allotted to each gang must be within its capacity, and this depends on the quality of the analysis which has previously been made of the capacity of a team in the pilot zone, and on the accuracy with which the country has been divided into zones of operation to be worked by such gangs Then it turns on the training of individuals, the regularity of their supply organisation and the quality of the supervision to which they are subject The requirements for training have been described In each region there should be a store carrying an ample reserve of apparatus and materials Supervision falls on the foreman of the gang, the inspector in charge of several gangs, the regional director and the central organisation, each of whom must accept responsibility and undertake both routine and surprise inspections The objectives of inspection are two, to ensure that the work prescribed is actually carried out, and to ensure that it is achieving the result intended, and their dual nature should be kept quite clearly in mind Checking of execution requires that clear instructions should be given on what is to be done, with proper arrangement of daily and weekly schedules and

precise working instructions, and a proviso that any deviation *from routine practice is to be reported immediately*. A known schedule can be checked with relative ease. The quality of spraying can be checked by frequent visual inspection and by periodic chemical analysis of wall deposits to see if the amount present agrees with that expected. The result desired is cessation of transmission of malaria, the forms of check on which will change as the programme advances, taking first that of examination of blood films from infants and later moving on to the various processes of surveillance.

Surveillance is built on the spraying programme at an early stage, and for a time the two overlap. It is a process of case-finding, the outline of which has already been described and the form of which will differ from scheme to scheme, though the element of specific house-to-house search both at random and where cases are suspected will remain important in each. Success cannot be hoped for unless public co-operation is achieved and there should be at this stage a considerable educative campaign *in which the objects* and methods of the scheme are described and co-operation sought, both in its passive form of acceptance of work and actively by assistance in the search for cases. The legal powers behind the scheme should rarely be brought into use, being reserved for dealing with intractable individuals who might by their opposition wreck some part of the programme.

This surveillance is the indicator on which progress is judged and on the findings of which other parts of the programme are modified. General spraying is discontin... has stopped and the reservoir of infective ...
that is, when no evidence of fresh ...
little evidence of ... of infection ...
number of resid... naturally
be taken. The p... then
search for ...
malaria ... on
has ended and ...
the disease to re-...
against the an...

adequate surveillance system has not discovered any evidence of transmission or residual endemicity, despite careful search, for three years in at least two of which no specific general measures of anopheline control have been practised The Expert Committee's requirements to establish the claim in relation to any specific area are that there should be —

(*a*) Proof that an adequate surveillance system has existed in the area for at least three years, in two of which no specific anopheline control measures have been carried out Any claim based on a lesser period of post-operational surveillance would need to be supported by proof of a surveillance mechanism above the usual quality,

(*b*) Evidence that in this period of three years no indigenous cases originating within that time have been discovered,

(*c*) Evidence of a register of malaria cases discovered during that time, it being established beyond reasonable doubt that each case was either

  (i) Imported, as shown by tracing the case to its origin in an acknowledged malarious area, or

  (ii) A relapse of a pre-existing infection, as shown by the history of the case and the absence of any associated cases in the neighbourhood of its origin, or

  (iii) Induced, as shown by its relation to a blood transfusion within an appropriate interval, or to another form of parenteral inoculation to which infection could be properly attributed, or

  (iv) Directly secondary to a known imported case

The last proviso allows for the fact that imported cases may occur anywhere and that a very limited spread may happen around them even in what would normally be non-malarious terrain, as for instance in England A secondary case derived from an imported case might therefore be overlooked though further generations of cases from this secondary would indicate an

established endemicity which would be incompatible with a claim of eradication.

On achievement of eradication the scheme as such comes to an end, but the search for cases must continue and measures must be taken if they are found. These activities would normally become a function of the Public Health Department and the special Division of Malaria Eradication would close. Foresight should be used to ensure that this does not mean the dispersal of staff, and if it is not used the staff will foresee the risk and may abandon the scheme before it is complete, choosing their own convenience in going rather than that of the organisation. This real risk can be overcome only by progressive integration of the eradication programme into the general public health programme during its later stages, and material advantages both to the staff and government can be gained by such integration. The eradication programme will inevitably have required sound epidemiological understanding and high standards of routine work, which are assets in any department and can form the background for other advances in the public health. The point that the eradication programme, though temporarily distinct, is an activity of the Public Health Department and one of a series of moves towards the creation of a healthy environment, cannot therefore be made too early or too forcibly.

The concept of eradication owes much to WHO, and its practice to that organisation and UNICEF, whose advice and help should be sought when any programme is considered. The Sixth Report of the WHO Expert Committee on Malaria deals extensively with the subject and is a proper guide which the reader who is to go fully into the subject is advised to consult.

VECTOR ERADICATION

The complete eradication of the anopheline vector from an area would of course achieve the eradication of malaria, though by a different route. The objective in an anopheline eradication programme is the destruction of a sufficient proportion of mosquitoes to ensure that each successive generation is smaller than the last, in fact to reduce the net reproduction rate below 1·0.

The fertility of anophelines is very high In many species the female may lay about 200 eggs five days after emergence from the pupa, and may repeat the process every couple of days up to 5 or more times during the course of an average lifetime Very little is known of the fate of the majority of these, but it seems that the biggest curb to multiplication is probably in the aquatic stage when the mortality is usually very high This is probably, however, caused by factors which are related to the density of larvae, it therefore decreases markedly as the larval density is thinned, after which a high proportion of eggs laid may result in the emergence of adults An eradication campaign through larvicidal attack must therefore aim at killing a very high proportion of all larvae, and provide for the recognition and treatment of the most minute and inaccessible breeding places A campaign based on the destruction of adults would have to achieve continuously a mortality of about 70–80 per cent of anophelines per day if it were to attain its purpose

Initial eradication schemes used the larvicidal attack and were first directed against the vector of yellow fever, *Aedes aegypti*, but later developed for the eradication of *Anopheles gambiae* in territories which it had freshly invaded The technical processes involved are not different from those of ordinary control, consisting of the application of any known larvicide which may be appropriate to the circumstances Essentially the procedure is an administrative one which attempts to ensure that within a large geographical area all breeding places without exception are treated, and that the work is checked to ensure that this is actually achieved The process consists first in the division of the territories into areas commonly called zones, of such a size that one small gang of men can treat all breeding places within one in the course of a working week The arrangement of these zones demands considerable care, probable readjustment after initial description, and demarcation on the ground so that the boundaries are visible to the workers Appropriate programmes of work are laid out for these zones and are checked by two means searches for larvae and searches for adults The searches for larvae, carried out on the day following that on which any particular area should have been

treated, are intended to check that the treatment prescribed was actually applied Searches for adults are carried out throughout the area and are intended to discover if there is any residual emergence, whether from known or from previously unrecognised breeding places The discovery of adults of the species leads to the assumption that untreated or inadequately treated breeding places still exist, and so to a concentrated search for them and to their elimination Programmes of this nature were carried out in Brazil following the migration of *A gambiae* from Africa and its multiplication over a part of that country, and in Egypt following the invasion of the lower Nile Valley by *A gambiae* from the Sudan In both cases the programmes were rapidly and completely successful, virtual elimination being secured within a year of the deployment of the full force intended The process was repeated in Cyprus with the purpose of eradicating the indigenous vectors of the disease, *A sacharovi*, *A superpictus* and *A claviger*, and it was thought that success was achieved A similar programme was carried out against *A labranchiae* in Sardinia and failed to secure the complete eradication of that mosquito, though it did achieve its reduction to extremely small numbers, from which the species has never since recovered to establish itself as a widespread mosquito This proclaimed failure did, however, to some extent discredit the technique as generally applicable Perhaps, however, it was too readily abandoned

Eradication of anopheline species by attack on the adults has been achieved in a few places, the first success being the eradication of *A darlingi* from a large part of British Guiana following a programme which was intended only to control it Since then *A darlingi* has been eradicated by similar techniques from many parts of South America Subsequent success has, again incidentally, been achieved in the eradication of *A funestus* in Mauritius, in a large part of Madasgascar, and in some localised areas of the Belgian Congo The common Italian vector of malaria, *A labranchiae*, has disappeared from large areas which it previously infested, and the control campaign in Ceylon has resulted in the local eradication of *A culicifacies* from some of the infested districts On the other hand there is ample evidence that thorough

programmes carried out against most of the other malaria vectors of the world have not achieved this eradication, and the mosquito concerned may multiply rapidly once control is ended Eradication therefore seems possible under limited circumstances which are favourable for ensuring a continuous high mortality amongst the mosquitoes This probably can only happen when the species is strictly endophilic, resting in houses every day and thereby coming into constant and repeated contact with insecticide Even when the species is highly endophilic a sufficiently high mortality is probably not always achieved The initial successes in British Guiana followed treatment of houses most of which were made of an impermeable hardwood often covered with paper, which probably provided an ideal background for the insecticide and combined with the high endophily of *A darlingi* to secure the unexpected result The objective of anopheline eradication by imagicidal attack is therefore not to be undertaken without either previous experience with the species concerned or considerable experimental background, but it is a concept to be borne in mind and progress towards which should be watched in any large insecticidal campaign to see if it is being approached and might be reached by some modification of technique

Even partial success in producing the near eradication of a species may be of great value for it has been found that the subsequent multiplication of species may be very much slower than had been expected An unexpected keenness of rivalry between species has been demonstrated, resulting in the usurpation of abandoned breeding places by other species which in some way preclude re-invasion by the original one We know too little about this to say it might be general, but it has been noted in Sardinia and in other places

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CHAPTER XIV

ANOPHELINE SUSCEPTIBILITY AND RESISTANCE TO INSECTICIDES

The toxicity of a chemical to an insect is only one of several factors which will determine its value as an insecticide, such as stability and persistence, volatility, and reaction of the chemical with wall surfaces, the degree of repellence or later irritation which it exerts, and other qualities The measurement of insect susceptibility must therefore be in terms of doses and periods of exposure which are not directly transferable to the field and may even be no useful guide to field practice Properly carried out, however, it gives data on the proportion dying following standardised exposure to different doses of the material, from which a range of lethal concentrations can be calculated and used for comparison between the susceptibilities of different species, or of the same species in different times and places The procedure of the test must be arranged to reduce the variables to the minimum possible and preferably to one only, the dose of insecticide, and in order that the work of different observers should be comparable it is most desirable that a rigidly standardised technique should be generally accepted That devised by Busvine and Nash and described in detail in Appendix II has been widely adopted, and involves the holding of insects in contact with filter papers impregnated with different concentrations of the insecticide for a standard period of time

This technique has now been used for some years and data on anophelines have been collected from several parts of the world Table 5 shows the median lethal concentrations of a range of insecticides to a laboratory bred colony of *A gambiae* tested by a carefully controlled technique There is sufficient divergence from this spectrum in other species to make the local estimation of normal susceptibility necessary, but at the same time records show that susceptibility is of the general order displayed by this colony, which represents a common pattern

TABLE 5

Median lethal concentrations of insecticides to normally susceptible female Anopheles gambiae *exposed in the standard Busvine–Nash test*

[Data from Davidson G (1956) *Nature* 29 September]

Insecticide	*M L C*
DDT	0·6%
γBHC	0·007%
Dieldrin	0·08%
Aldrin	0·2%
Malathion	0·8%
Pyrethrins	0·4%

An hereditarily transmitted decrease in susceptibility following repeated exposure to insecticides was an acknowledged phenomenon before the advent of the chlorinated hydrocarbons, being known to occur in several agricultural pests and in one case amounting to tolerance of hydrocyanic acid The first records concerning insects of medical importance came in 1946 and concerned the development of resistance to DDT by the housefly in Italy These reports were rapidly followed by others from many parts of Europe and America, and led to laboratory experiments in which it was demonstrated that exposure of successive generations of flies to DDT led to a steadily progressive decrease in susceptibility until resistance might amount to several hundred times the normal It became clear that this resistance was likely to develop in the housefly in any area where any of the chlorinated hydrocarbons were used systematically for its control, and might be expected to rise to such a degree that control would be nullified It was also demonstrated that the chlorinated hydrocarbons fell into two groups the one including DDT and its analogues methoxychlor and DDD, the other chlordane, aldrin, dieldrin γBHC, isodrin and endrin Resistance to a member of one of these groups extended to the other members of the same group but not to those of the other group Thus resistance to DDT extended to methoxychlor but not to γBHC, while resistance to the latter extended to dieldrin and other members of the group but not to DDT It appears that within one group the relative degrees

of resistance to the different insecticides are independent of the material which selected resistance, in the second group it arises least against endrin and in progressively increasing degree against isodrin, γBHC, dieldrin, aldrin and chlordane

Resistance has since been recorded successively in one place or another amongst other insects of medical importance, in *Culex pipiens*, in four species of salt marsh mosquito *Aedes taeniorhynchus*, *Aedes sollicitans*, *Aedes nigromaculus* and *Culex tarsalis*, in *Aedes aegypti* in one locality—Trinidad, in the louse, bed-bug, cockroach and some anophelines Though the records of these are definite it is to be noted that no insect has acquired resistance with the frequency and facility displayed by the housefly, which is the only one to show itself generally able to resist attack through this mechanism

There are probably many varieties of resistance, falling into two main types behaviouristic and physiological The behaviouristic form is manifested by modification of habit in such a way that the insect rests less commonly or for shorter periods on treated surfaces, and thus runs less risk of poisoning though its susceptibility has not decreased Only one example in the anopheline has been fully documented, in *A albitarsis* in Panama, but it has been suspected in other instances notably amongst *A gambiae* in both Mauritius and Madagascar, though there are insufficient data from these places on which to establish clear proof of a change of habit It may well have occurred by selection of a predominantly exophilic strain, but in the case of *A gambiae* at least the importance of the alleged phenomenon is balanced by the fact that the persistent strain is not a potent vector, apparently owing to a common choice of animal blood in preference to human

There are doubtless several types of physiological resistance which may be acquired under different circumstances, and which may be broadly classified as vigour-tolerance and specific resistance Susceptibility of the mosquito varies with its stage of nutrition, with the lapse of time since the last blood feed, with the previous nutrition of the larva with other factors, and in general with the vigour of the insect Repeated laboratory exposure of succeeding generations of insects to insecticides may produce a

progressive increase of tolerance which in some cases does not seem to be due to any specific ability to degrade or otherwise dispose of the material. The enhancement of tolerance is usually of a small order, two to five times, and may well occur in nature. It is not known that it has interfered with the success of malaria control or other public health measures. There is another type of resistance, often marked by great increase in tolerance, which is due to a specific ability to degrade or otherwise detoxify the insecticide. The following description concerns this specific physiological resistance, which has in fact interfered with many public health programmes, including malaria control schemes.

The first report of its occurrence amongst anophelines came in 1951, concerning *A. sacharovi* which was later confirmed to be resistant to DDT in parts of Greece. DDT had been widely used as both a larvicide and imagicide since 1944, the appearance of resistance was certainly long delayed, and was only given numerical values in 1954 and 1955 when median lethal concentrations of 1.7 and 3.0 per cent DDT, roughly three and six times the normal, were recorded. Further reports from Greece concerned the development of resistance by this species to chlordane, and its appearance to both these insecticides in *A. superpictus*. *A. sacharovi* also became resistant to DDT in a small part of the Lebanon, the median lethal concentration being raised about three times, but the mosquito was later eradicated from this same area by the application of dieldrin. *A. sundaicus* developed resistance to DDT in three parts of Indonesia where it had been exposed to both larvicidal and imagicidal practice, and it was found on examination in 1955 to be able to tolerate about eighteen times the usual concentration of DDT, but to remain normally susceptible to dieldrin and γBHC, a pattern reproduced in *A. stephensi* in a part of Saudi Arabia where tolerance of DDT was enhanced ten times. The converse pattern, resistance to dieldrin and γBHC but not to DDT, was found in 1954 amongst *A. quadrimaculatus* in an area in Mississippi where breeding places had been freely contaminated with dieldrin used as an agricultural insecticide. A further record of this same type came from Northern Nigeria where in 1955 Elliott and Ramakrishna recorded

an eight times enhancement of the resistance of *A gambiae* to dieldrin following 12 to 18 months' exposure to that insecticide used in an imagicidal campaign

Whilst these records of resistance amongst anophelines are numerous and disturbing, it is to be realised that they have occurred on a background of insecticidal practice which is enormous in scale Throughout most of the areas where it has been carried out, often for 8 or 10 years, resistance has not been suspected Though the quality of resistance in the anopheline resembles that in the housefly, the facility of its production is on a very different scale

Two separate colonies of resistant *A gambiae* and one colony of resistant *A sundaicus* were established in the Ross Institute in London during 1956 The establishment of colonies, in this case for the first time, permits accurate study which at the time of writing is still very young Nevertheless some extremely important points have emerged In the original colony of *A gambiae* resistance had been produced by exposure to dieldrin, and in the second colony by exposure to γBHC Both of these showed the same spectrum of resistance, greatly enhanced to chlordane, dieldrin, isodrin, endrin and γBHC, and in that order of degree and not enhanced to DDT or methoxychlor Taken with the findings in other groups of insects, and by the same worker in anophelines in Indonesia and Saudi Arabia this may be taken to establish a general case Specific physiological resistance covers one or the other of these two groups of insecticides without necessary cross-resistance to the other Resistance to dieldrin implies resistance to γBHC but not to DDT, and vice versa

These same colonies have been submitted to genetic studies, in which a great variety of crosses have been made between anophelines of resistant, susceptible, and hybrid strains to determine the nature of inheritance and thus of selection of resistance In *A gambiae* only, three grades of resistance can be recognised and these three are quite distinct from each other without any gradual progression from one to another They are the fully susceptible, the fully resistant, and the hybrid Inheritance of the characteristic follows the pattern associated with a single

pair of genes, described as monofactorial, in which neither has marked dominance The homozygote resistant (**rr**) breeds true to type and has a tolerance to dieldrin about 800 times the normal, and to γBHC about thirty times When crossed with a homozygote susceptible (**ss**) it produces a heterozygote hybrid (**rs**) with over thirty times the normal tolerance to dieldrin and over seven times the normal to γBHC The progeny of this heterozygote (**rs**) crossed with either of the homozygous strains (**rr** or **rs**) have the sharply defined characteristics of two of the three types, and these types occur in the proportions associated with monofactorial inheritance The crossing and classification of progeny has been so elaborate and has produced such consistent results that the monofactorial inheritance of this type of specific physiological resistance can be taken as firmly established

Individual insects correspond to one of three types **rr**, **rs** or ss, each of which has sharply defined characteristics In each case mortality on exposure to insecticides is distributed in a random manner around a median lethal concentration In the case of dieldrin the three median lethal concentrations, and the scatter of mortality around them, are so far separate from each other that it is possible to prescribe *discriminating doses*, the lower of which will kill all ss individuals but not **rs** or **rr** specimens, and the higher of which will kill all ss and **rs** individuals but leave **rr** insects unscathed Appropriate discriminating doses in this original work on *A gambiae* have proved to be 0 4 and 4 per cent dieldrin, to which insects are exposed by the standard Busvine and Nash technique, for one hour to 0 4 per cent and for two hours to 4 per cent Equivalent discriminating doses of γBHC can be established and have been used, 0 025 and 0 1 per cent, but the margin between them is less, the chance of error therefore greater, and they are unnecessary because γBHC resistance is coupled with dieldrin resistance

By the use of these discriminating doses it is possible to find the proportions of the three types, ss, **rs** and **rr**, in any collection of living mosquitoes, this has been done on a large scale in the laboratory and already on a practical scale in the field This gives rise to the concept of the *detectable* gene of resistance It has

been shown that the gene can be readily detected in this way in places where no selection by insecticides has been carried out, the percentage of anophelines carrying it having varied between 0 04 and 6 in the part of Northern Nigeria where the work was done It is expected, however, that in some other places the gene will prove to be absent From this there develops the prospect of mapping potential resistance which would be selected by the application of insecticides to produce wide general resistance There are many questions concerning the rate of such selection, the dissemination of resistance around a point of selection, and the fate of the gene on cessation of selection to which an answer would now be either impossible or have little more standing than a guess, but the mechanism of approach is valid and could clarify them all

Extension of this mapping progress is already projected, but to facilitate it some modification of technique is desirable because the small tubes of the Busvine and Nash technique are not well adapted to large scale work with many mosquitoes and because the impregnation of the papers often presents difficulties to the field worker These obstacles are being overcome by enlargement of the tube and the preparation of pre-treated papers, both of which demand time for testing before they can become standard A revised test based on these principles is now being prepared and will form the basis of field mapping

It is rare for a gene to cause modification in one characteristic only, and two variations from normal in the colonies and crosses used in this work have therefore been of great interest though their status still needs final confirmation They are an enhanced vigour in the homozygote **rr**, and some infertility in the heterozygote, or **rs** individual All three of the pure resistant colonies are abnormally vigorous and easy to maintain, and the individuals are long lived and hardy In many of the crosses it has been found that the male **rs** is either completely or relatively infertile with the result that mutual crossing within the heterozygote group is either impossible or relatively infrequent These subjects are still under study at the time of writing, but they both probably have some association with resistance and the infertility may perhaps

be subject to cytoplasmic inheritance. However that may be, the existence of these two characteristics which have opposing influences on the chance of survival of the carrier make it impossible to forecast the fate of the gene, and a field elaboration of research on this subject is much needed to clarify it.

Comparable studies of the colonies of *A. sundaicus*, one of which is resistant to DDT, show that inheritance of this resistance is also monofactorial, with some difference of detail. In the fully susceptible strain the median lethal concentration of DDT, determined by the Busvine and Nash technique, is about 0·5 per cent., and all members are killed by 2·0 per cent. DDT. The majority of the resistant strain survive exposure to 4·0 per cent. DDT for several hours, their tolerance being increased about fifty times. Hybrids between the two are only slightly more resistant than the susceptible strain, and it is not practicable to insert a discriminating dose which would kill all susceptible insects and allow all hybrids to survive. It is probable that this low tolerance by hybrid mosquitoes results in their being killed in the field by normal applications of DDT, and causes the very much slower development of resistance to DDT in nature. The spectrum of resistance is the reverse of that displayed by the *A. gambiae* colonies, the resistant strain of *A. sundaicus* surviving exposure to DDT but being normally susceptible to dieldrin and other members of the same group, a point proved in the field by the successful control of DDT resistant *A. sundaicus* by dieldrin formulations.

A suitable concentration of DDT to separate resistant individuals from both hybrids and susceptibles is 2·5 per cent. Tolerance of this dose by many specimens would indicate resistance; tolerance by a few should lead to a suspicion of it, and verification in the laboratory should be attempted. The immediate progeny of a resistant female fertilised by an unknown male might consist of **rr**, both **rr** and **rs**, or only **rs** individuals. The first two of these groups could be recognized, but not the third. Further progeny, however, from such an **rs** group would include 25 per cent of **rr** members which could be distinguished.

The occurrence of resistance, the discovery that it is possible to detect the gene even when present in very small numbers, and the fact that the technique of detection is relatively simple, indicate a definite line of field activity which should be incorporated in all survey work. It should be the function of a base laboratory to measure the complete range of susceptibility of the species of mosquito concerned, as it is before exposure to selection or as soon thereafter as possible, for which the technique described in Appendix II may be used. This susceptibility should be expressible as a straight line when dose-mortality results are entered on probit paper. Should there be any abnormality, in the form of unexpected survival of some mosquitoes at the higher doses in numbers not consonant with a straight probit line, survivors should be kept and an effort made to obtain eggs from them. Their progeny in turn should be tested and their adherence to the original pattern or deviation from it will indicate whether their survival was a random matter or due to the effect of some resistant gene.

In this way it should be possible for the base laboratory to prepare a probit line for homozygote susceptible, ss, members of the species. A discriminating dose can then be selected which is slightly above the lowest that would kill all of this group. In the case of *A. gambiae* and dieldrin this dose is 0.4 per cent., in the case of *A. sundaicus* and DDT it is 2.5 per cent. Away from the base laboratory field workers need use this discriminating dose only, recording the numbers of mosquitoes exposed to it and the numbers dying. The deaths should be 100 per cent. of exposures if no resistant gene is present and the basic data are correct. Initially it may be necessary to check this last point by saving any survivors and dispatching them to the base laboratory for collection of eggs and if possible rearing and examination of progeny. Once the data are established, survivors may be taken as evidence of the presence of the resistant gene, which may be mapped by the proportions in which it occurs in different localities. Where it is relatively numerous tests might be elaborated by addition of the second, higher, discriminatory dose of dieldrin when the proportions of **ss**, **rs** and **rr** individuals could be defined.

Any major control scheme should be accompanied in its early stages, or preceded, by an examination of the susceptibility of the anopheline, which should take the form of the laboratory determination of the probit curve and field examinations of large numbers by means of the discriminatory dose to see if any evidence of the existence of resistant specimens can be found If any *prima facie* evidence is found it should be taken as demanding further urgent study on which all available laboratory resources might well be concentrated If it is confirmed, further studies should concern the spectrum of resistance and the form of its inheritance both of which are likely to follow the pattern previously described The problem of imagicidal control will then at least be presented in clear terms to the operator

Once a material degree of resistance has developed in the course *of a campaign the operator is faced with a very serious position* All possible methods of investigation of the nature, degree and spectrum of the resistance should be brought into action Every effort should be made to establish a resistant colony for full analysis of its character If there is interference with control a change must be made to an insecticide for which no resistant gene is present, and rapid eradication of malaria should be attempted with its aid

The occurrence in a population of the gene structure which may lead to selection of a resistant group is a matter of pure chance In the fly population the risk is high and in the anopheline *population it is low There is no genetic reason* to believe that prolongation of practice will necessarily lead to progressively increasing resistance, though any resistant mutant arising during its course would be at an advantage and able to multiply its kind rapidly

If the appropriate gene structure exists the selection of a resistant strain is perhaps inevitable, but the period of time within which it will be developed must turn considerably on the efficiency of the selection process It is freely said that relatively inefficient schemes are to be discouraged as they may specially favour the development of resistance, and also that a series of small schemes should be discouraged for the same reason in

favour of larger schemes Knowledge of this phenomenon is inadequate for proper forecasting but there does not appear to be any justification in either of these speculations Rapidity of selection is likely to be in direct proportion to the efficiency of the scheme, to the size of the area it covers, and to the duration of insecticidal attack, all of them influencing as they do the probability of dilution of resistant groups by susceptible populations It has also been said that combination of larvicidal and imagicidal practice has greater dangers than either alone The circumstantial evidence which led to this was inadequate and has not been reinforced by the passage of time, while laboratory experiment has lent no support The only justification that remains is the fact that the combination might be more efficient than one alone and so carry a greater risk of selection The real ground for discouragement of this practice, however, lies in the lack of need for the two when one alone can secure control

The chief lines of study of resistance which hold out promise of having practical value are efforts to discover the resistant gene before artificial selection has made it widespread, further analysis of the genetic character of resistance and of associated factors, examination of the speed of development of resistance when artificial selection is practised, further analysis of the relationship between resistance to different insecticides, and inquiry into the mortality amongst **rs** and **rr** individuals following various insecticidal regimes

A statement on anopheline resistance written at the present time cannot be more than tentative because factual knowledge is still in an elementary state It does seem that the fear of resistance should be no impediment to the establishment of small schemes of control, and that it should not be used as a background on which to restrict the use of insecticides by individuals or by small communities which may not be able to attain high standards of efficiency It is clearly imperative that any major scheme should be associated with systematic and rational studies of the subject There is no known technique by which the risk of development can be avoided if the gene is present but it would seem wise to concentrate in any major scheme on one insecticide, or if more

were needed solely on insecticides within one of the two groups which have been described, to minimise the risk of development of resistance to both On the occurrence of resistance to one there would then be the opportunity for a reconsideration of the scheme and substitution of the use of a member of the other group in a campaign designed to bring malaria to an end before a second resistance could develop The appearance of resistance is a valid reason for attempting to convert a control programme into an eradication campaign but it does not justify any panic based on the suggestion that the universal development of resistance may be near at hand It would seem that the development has been by chance in particular localities and is likely to continue by chance, with no particular technique of application and no particular insecticide to be blamed for its appearance

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APPENDIX I

MATHEMATICAL STATEMENT

THE object of mathematical analysis is to prepare models showing how the various factors concerned in transmission interact with each other to build up a composite picture of endemic or epidemic conditions resembling that seen in nature If it does so it has succeeded in that it has facilitated understanding of happenings and of the factors which control the order of events It is no part of the function of analysis to attempt a prediction in precise terms of the number of cases to be expected in any particular set of circumstances, and it is improbable that the factors concerned could be known with sufficient accuracy to make such a prediction The approach is now long established, and has been recently and excellently reviewed by Serfling and by Bayley Starting about a century ago it has been refined in recent years by the substitution of a stochastic approach for the deterministic one with which it started and was developed The essential difference is that the latter deals with the subject as if there were no random error from the expected form of events, while the stochastic approach makes allowance for deviations inevitable in small groups The latter is the more realistic of the two, the differences between which are roughly inverse to the size of the groups or cells within which infection takes place When these are small, as in family infections, the stochastic method may be the only one giving models resembling natural happenings though when the groups are large the deterministic approach can reproduce happenings within acceptable limits of error This particularly applies when dissemination is to a community as a whole by an insect which moves freely from house to house in the interval between acquiring infection and passing it on There would be very considerable difficulty in the application of a stochastic technique to the very complicated picture of malaria transmission with its large number of variables, it has not yet been undertaken and since the deterministic method gives reliable pictures it is doubtful if the effort would be justified

The disease to be analysed must first be established by criteria of recognition, and the criterion of malaria here used is the presence in the peripheral blood of parasites which are demonstrable by normal techniques The variables to be considered relate to man, the disease and man's reaction to it, and the mode of transmission to man When transmission is from man to man *via* an insect host the additional variables which come into play are the expectation of life of the insect,

the frequency of its biting man, and the period of infection in the insect with the latter's reaction to it

The main relevant variables in man are the mortality to which he is subject and the amount of migration to and from the district considered Allowance was made for these in the original development of a mathematical model of malaria by Ross, and for mortality by the original working on malaria by the present author It was found by practical working that mortality on the scale which happens in nature made so little difference to the values of parasite rates that the considerable extra complication involved by their inclusion was not justified and no subsequent attention has been paid to it There are however fields in which the effect of migration and natality may be considerable in the changes of communal immunity leading to cyclical epidemics and in the establishment of communal immunity leading to the hyperendemic state No detailed mathematical analysis of this has yet been attempted though the general implications of varying mortality, natality and migration on them have been roughly seen It remains a field for further analysis which might be fruitful

The variables related to the disease in man and his reaction are the incubation period, the pattern and probability of recovery the pattern of infectivity, which may be different from that of disease manifestation and the immune response in terms of recovery and protection against re infection or against superinfection The points of relevant interest are that the probability of recovery from malaria can be reasonably expressed as a simple recovery rate the incubation periods of falciparum malaria and of infectivity in that condition are materially different from each other, as are recovery rates from the disease and infectivity, and that it is reasonable to treat malaria as a disease in which superinfection can occur The present analysis differs from previous ones in making this allowance which appears to be vital to the formation of realistic models, and for which a justification was produced in one of the original publications on the subject

The relevant variables in the mosquito are its numbers, its expectation of life and its habit of biting man The present analysis makes allowance for variability in expectation of life and for a connection between that expectation and the prospect of survival for a period sufficient for parasites to develop within it, differing in this way from its predecessors Mosquito mortality is looked on as a constant independent of the age of the insect, it being considered that in nature the hazards of daily existence which fall alike on insects of all ages are more important than the processes of degeneration leading to death from some degree of old age Again as an absolute truth this cannot be substantiated but a review of knowledge suggests strongly that it approximates reasonably to truth, and sufficiently to form a basis for

sidered as an average value then the concepts and the relationships founded on it remain firm

The variables of the disease in relation to the mosquito are the incubation period of infectivity within the mosquito, the duration of infectivity, and the effect of infection on the mosquito's viability The first is considered as a function of temperature and species of parasite in a form illustrated in Figure 1 Infectivity of the mosquito is looked on as permanent once established, and no influence on viability is recognised There is a further variable, the proportion of bites by infected mosquitoes which actually inoculate infections which develop in man It has been allowed for in all expressions and field working suggests that it may have a very variable value, ranging from nearly 1 0 to 0 01 or conceivably less The extent to which it is dependent on characters of the mosquito, of the infection in it and especially the density of that infection, and of the immune state of the recipient, cannot be deciphered though the density of infection is looked upon as important

SYMBOLS USED IN ANALYSIS

m the anopheline density in relation to man

a the average number of men bitten by one mosquito in one day

b the proportion of those anophelines with sporozoites in their glands which are actually infective

p the probability of a mosquito surviving through one whole day

n the time taken for completion of the extrinsic cycle

s the proportion of mosquitoes with sporozoites in their salivary glands

h the proportion of the population receiving inocula in one day

x the proportion of people affected (that is, showing parasitaemia)

L the limiting value of the proportion of men infected when equilibrium is reached

r the proportion of affected people, who have received one infective inoculum only, who revert to the unaffected state in one day

t the time in days from the start of the incubation interval referred to

e the base of natural logarithms, 2 71828

i the average time in days from ingestion of gametocytes by an anopheline to the development of infective gametocytes in a second case infected by it Successive intervals of this duration

are designated t_0, t_1, t_2, etc In wording, the period is ref
to as the incubation interval

y the proportion of total time lived, within one incubation inter
in which the population is infective, or

$$\frac{1}{t}\int_{t=0}^{t=t} x\,dt$$

z the reproduction rate, or number of secondary infections distri
buted by a single primary case, and

z_0 the limit of z as x approaches zero, or basic reproduction rate

EXPRESSIONS OF MOSQUITO LIFE

The probability of surviving through n days is

$$p^n$$

The expectation of life is

$$\frac{1}{-\log_e p}$$

The expectation of life after surviving through n days is

$$\frac{p^n}{-\log_e p}$$

THE PROPORTION OF MOSQUITOES WHICH ARE INFECTIVE

This is commonly described in terms of a percentage as the sporozoite rate, but here as a proportion Bearing in mind that a mosquito cannot have sporozoites in its salivary glands until after the completion of n days the probability of this happening on the following day will be a reflection of the probabilities of its having taken an infective feed on the first day of its life The probabilities for the day which follows will reflect the infective feeds on the first and second days *less* the possibility of one infective feed being masked by a previous one The converse of this, the probability of *not* having sporozoites on day n $n+1$, etc, can be easily understood By this means and by reference to the previous section it is simple to establish the following values —

The expectation of life, already stated as

$$\frac{1}{-\log_e p}$$

(see 2)

MATHEMATICAL STATEMENT

THE PROPORTION OF PEOPLE INFECTED

It is first necessary to examine conditions as they would be if inoculation rate were constant, independent of the proportion of peop affected. This is an essential step in analysis and also reflects natur happenings amongst infants born into a malarious community, and ma be considered as a statement of the infant parasite rate in endemic conditions. The analysis is based on that prepared by Ross, and in its elaboration that author had the generous help of Dr. J. O. Irwin.

It will be noted in the statement of symbols used that the recovery rate, r, is described as the proportion of people *who have received one infective inoculum only*, who revert to the unaffected state in one day. When subject to constant risk of infection according to an inoculation rate h, infected individuals may have received more than one infective inoculum, and it has been shown that when superinfection occurs the actual probability of recovery of an individual exposed to such risk (R) can be expressed as:

$$R = r - h \qquad (10)$$

with a limiting value of zero when h exceeds r. As a consequence of this change in the actual proportion of recoveries, two forms of expression must be developed for x, the proportion of people affected, according to the relative values of h and r.

The form of working need not be repeated as it is directly derived from that of Ross, which has often been reproduced and is well known. It can be shown that if superinfection is admitted and the consequent adjustment in the proportion of recoveries made, then:

When h is less than r

$$\frac{dx}{dt} = h - rx \qquad (11)$$

and the value of x will gravitate to a limit

$$L = \frac{h}{r} \qquad (12)$$

and that at any time x may be expressed as

$$x = L - (L - x_0)e^{-rt} \qquad (13)$$

where x_0 is the value of x at time t_0 and that

When h equals or exceeds r, the value of x will gravitate to the limit 1·0, and can be expressed at any time as

$$x = 1 - (1 - x_0)e^{-ht} \qquad (14)$$

while

$$\frac{dx}{dt} = h(1 - x) \qquad (15)$$

THE PROPORTION OF PEOPLE INFECTED

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while

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The transition from one form to another is quite smooth and simple in synthetic working though it may cause confusion in analytical work It is sometimes of value to note the time at which values less than the limit are reached, as it helps in the examination of simple curves It is illustrated in the following table, in which K represents either r or h, whichever is the greater.

Time at which succeeding stages in the curve are reached

Value of x	Time, t
0 1 L	0 197/K
0 2 L	0 207/K
0 3 L	0 358/K
0 4 L	0 511/K
0 5 L	0 693/K
0 6 L	0 917/K
0 7 L	1 21/K
0 8 L	1 61/K
0 9 L	2 30/K
0 95 L	3 02/K
0 975 L	3 69/K
0 99 L	4 60/K

When infant parasite rates grouped by ages are available, and fall into a curve such as represented by one of these expressions, then it is possible to derive from them an estimate of the inoculation rate, h, which is reasonably free from error When they gravitate to a limit less than 1 0, then the value of that limit as given in (12) may be transposed to read

$$h = r\mathrm{L} \qquad (16)$$

It is often reasonable to assume a value of 0 005 for r in using this, and the assumption can be checked or a better estimate made by examination of earlier values of x and use of the identity

$$r = \frac{-\log_e(\mathrm{L}-x)}{t} \qquad (17)$$

which is derived from (13) and in which t is the time in days from birth of the values of x chosen When the curve gravitates towards unity the value of h may be directly assessed from the expression, applied to earlier values

$$h = \frac{\log_e(1-x)}{t} \qquad (18)$$

This value of h may then be compared with that derived from entomological observation of m, a and s, and the value of b, the proportion of anophelines with sporozoites in their glands which is actually infective, can be derived from

$$b = \frac{h}{mas} \qquad (19)$$

which is a transposition of (8) Estimation of this value in the field has been found very fruitful

THE REPRODUCTION RATE

In the course of its time of infectivity ($1/r$) a case will be bitten each ly by ma mosquitoes of which the proportion not yet infected will be $(1 - ax/ax - \log_e p)$ The proportion of these surviving for n days is p^n, l their subsequent expectation of life is $\frac{1}{-\log_e p}$ During this time they will bite a times each day, and the proportion b of these bites will be infective, whence

$$z = \left(1 - \frac{ax}{ax - \log_e p}\right) \frac{ma^2bp^n}{-r \log_e p} \qquad (20)$$

(2) The limit of the above rate as x approaches zero is

$$\frac{ma^2bp^n}{-r \log_e p} \qquad (21)$$

which is termed the basic reproduction rate, designated z_0

The basic reproduction rate (21) is very much used in description, and with a value of r suitable for non immune people inserted in it, the reason being that as x approaches zero the restraining influence of immunity must approach the same level or, colloquially, control must be related to the reaction of a non immune population The normal value of the recovery rate attributed is 0 0125 thought to be representative of recovery from infectivity in falciparum infections It is appreciated that in nature the value of the reproduction rate is greatly influenced by immunity altering the values of r and b, and a method of approach to the ruling value of the rate may be developed in the following way —

It has already been shown that

$$s = \frac{p^n ax}{ax - \log_e p} \qquad \text{(see 7)}$$

and it will be shown that

$$L_x = \frac{mabp^n}{r} + \frac{\log_e p}{a} \qquad \text{(see 26)}$$

If this last expression is substituted in the expression for s above it can be shown that the limiting value of s is given by

$$L_s = \frac{p^n}{z_0}\left(z_0 - 1\right) \tag{22}$$

whence

$$z_0 = \frac{p^n}{p^n - L_s} \tag{23}$$

provided $x < 1 \cdot 0$

Hence, when conditions are static, it is possible to make an estimate of the ruling reproduction rate if the sporozoite rate, the probability of mosquito survival, and the time of extrinsic development of the parasite are known

EQUILIBRIUM, OR ENDEMIC VALUES OF PARASITE AND SPOROZOITE RATES

It has already been shown that when h does not exceed r

$$\frac{dx}{dt} = h - rx \qquad \text{(see 11)}$$

and in this there can be inserted the full expression for h given in (9) In such a combination, however, the values of x will refer to different values of t to give an expression

$$\frac{dx_2}{dt} = \frac{ma^2bx_1p^n}{ax_1 - \log_e p} - rx_2 \tag{24}$$

in which the forms x_1 and x_2 are used to indicate that they refer to values of x at different times separated by the time interval of the incubation period in the mosquito *plus* that in man When the limit of this expression is considered, this is immaterial because at that time x_2 and x_1 are by definition the same

When h equals or exceeds r

$$\frac{dx_2}{dt} = \frac{ma^2bx_1p^n(1 - x_2)}{ax_1 - \log_e p} \tag{25}$$

The first of these has two limits a finite one when

$$L_x = \frac{mabp^n}{r} + \frac{\log_e p}{a} \tag{26}$$

and also a limit of zero The limit is attained when

$$\frac{ax - \log_e p}{mp^n} = \frac{a^2b}{r} \tag{27}$$

This can be turned to give an explicit value of m for a constant known value of p, or an implicit value of p for constant known values of m

The second differential has a theoretical zero limit which is, however, incompatible with the prerequisite that h should equal or exceed r to make it operative, and a sole effective limit of 1·0

Expression (26) gives the limiting value of x when h does not exceed r, and it is of use in analysis to note that by the substitution of the value of z_0 given in (21) it may be simplified to read

$$L_x = \frac{-\log_e p}{a}(z_0 - 1) \qquad (28)$$

STABILITY OF EQUILIBRIUM

From (28) it can be readily derived that

$$\frac{d(L_x)}{dz_0} = \frac{-\log_e p}{a} \qquad (29)$$

which last is therefore a measure of the variation of L_x in association with that of z_0 or an index of sensitivity It may be noted that $a/-\log_e p$ indicates the average number of feeds taken on man in the course of a mosquito's life, and hence the statement that sensitivity is inversely dependent on this figure

It is from (29) that an index of stability is given in the text, showing as it does the degree of variation in the endemic level with variations in the reproduction rate as a whole It is of interest, however, to examine the influence of component parts of the reproduction rate on the endemic level in the form of a number of partial derivatives which are here reproduced

i In relation to changes in mosquito density

$$\frac{\partial L}{\partial m} = \frac{abp^n}{r} = \frac{La - \log_e p}{ma} \qquad (30)$$

which is modified to show the ratio of increase in L corresponding to a multiplication in m, to give an index of

$$L - \frac{\log_e p}{a} \qquad (31)$$

ii In relation to changes in probability of mosquito survival

$$\frac{\partial L}{\partial p} = \frac{mabnp^{n-1}}{r} + \frac{1}{ap} = \frac{n(La - \log_e p) + 1}{ap} \qquad (32)$$

iii In relation to changes in the period of the extrinsic cycle

$$\frac{\partial L}{\partial n} = \frac{p^n \log_e p\, mab}{r}$$

$$= \log_e p\left(L - \frac{\log_e p}{a}\right) \qquad (33)$$

(*N.B.*—This expression has a negative value)

iv In relation to changes in the man biting habit

$$\frac{\partial L}{\partial a} = \frac{mbp^n}{r} - \frac{\log_e p}{a^2}$$

$$= \frac{La - 2\log_e p}{a^2} \qquad (34)$$

v In relation to changes in the rate of recovery

$$\frac{\partial L}{\partial r} = \frac{-mabp^n}{r^2}$$

$$= -\frac{1}{r}\left(L - \frac{\log_e p}{a}\right) \qquad (35)$$

EPIDEMICS

The incubation interval plays a very large part in determining the form of epidemics Mathematically its very existence means that the epidemic cannot be represented by a single curve, but only by a series of linked curves each of the duration of one incubation interval Precise definition over several of these curves has been explored by Armitage but soon presents almost insurmountable complications A less exact description of events, with the advantage that it is somewhat simpler, is here reproduced, while a further and less exact simplification can, however, be permissibly used when examining the earliest stages of epidemics when x is low

Let it be assumed that malaria is endemic, a state of equilibrium having been reached, the value of x being low This pre existing equilibrium is expressed by

$$L = x_0 = \frac{mabp^n}{r} + \frac{\log_e p}{a} \quad \text{(already established)} \qquad (36)$$

and is due to an inoculation rate *mabs*, or

$$h = \frac{ma^2bp^nx_0}{ax_0 - \log_e p} \quad \text{(from value of } s\text{, already established)} \qquad (37)$$

$$= x_0 r \quad \left(\text{from the value } L = \frac{h}{r}\text{, already established}\right) \qquad (38)$$

from which it may be noted that:

$$ma^2bp^n = r(ax_0 - \log_e p) \qquad (39)$$

At a given time, starting the first incubation interval of a consecutive series, it is assumed that the value m, a or p is changed and that as a result the value of h is increased to ch, or cx_0r, during that interval. During the whole of it, however, there is no disturbance in the value of x, as by definition of i no secondary cases due to the increased value of h have yet occurred. Therefore $x_1 = x_0$. In the following interval, i_2, the value of x will show progressive increase. This increase will be in response to a static inoculation rate at its new higher value, ch. It is thus an independent happening and will follow the expression established for such, which taken with (38) reads:

$$x_2 = cx_0 - (cx_0 - x_0)e^{-rt} \qquad (40)$$

$$= x_0\{c - (c-1)e^{-rt}\} \qquad (41)$$

and

$$\int_{t=0}^{t=i} x_2 . dt = x_0 ci - \frac{x_0}{r}(c-1)(1-e^{-ri}) \qquad (42)$$

Since the total time lived in this interval is i days, and the number of infective days lived is given by (42), it follows that the proportion of time lived in which the subjects are infective is:

$$y = x_0 c - \frac{x_0}{ir}(c-1)(1-e^{-ri}) \qquad (43)$$

In the succeeding intervals, i_3, i_4, etc., the value of x again progressively increases, but now in response to a progressively increasing inoculation rate dependent on the value of x at the same stage in the previous incubation interval. The growth can be approximately studied as serial values of x at intervals of time i starting from any desired point by the following method.

The value of y_2 is given in (43). The mean inoculation rate derived from it is expressed by:

$$h_2 = \frac{ma^2bp^n y_2}{ay_2 - \log_e p} \qquad (44)$$

$$= \frac{r(ax_0 - \log_e p)y_2}{ay_2 - \log_e p} \qquad \text{(see (39))} \qquad (45)$$

This new inoculation rate may be used in the expression for the value of x at the end of the interval i_3 when $t = i$:

$$x_3 = \frac{h_2}{r} - \frac{1}{ir}\left(\frac{h_2 - 1}{r}\right)e^{-rt} \qquad (46)$$

The value of y_3 derived from this is

$$y_3 = \frac{h_2}{r} - \frac{1}{zr}\left(\frac{h_2-1}{z}\right)(1-e^{-rt}) \tag{47}$$

and in turn

$$h_3 = \frac{r(ax_0 - \log_e p)y_3}{ay_3 - \log_e p} \quad \text{(see (37) and (39))} \tag{48}$$

Approximate values of x at serial intervals can then be obtained by continuation of this process, and the derivative can be calculated at any point by the established expression

$$\frac{dx}{dt} = h - rx \tag{49}$$

At the point in this series when the value of h exceeds r a transfer must be made to the basic formula

$$x = 1-(1-x_0)e^{-ht} \quad \text{(already established)} \tag{50}$$

which demands a modification of technique, but no more

Epidemics have been synthesised on this basis and have produced models which give a very fair representation of natural happenings, and sufficiently so to establish the technique as representative of truth Undoubtedly, however, the work involved is considerable and rapid synthesis of numerous epidemics is not possible Such rapid synthesis was, however, required in an appreciation of the probable order of happenings to be expected following the re introduction of malaria to places from which it had been eradicated In exploring the origins of such epidemics, when x is low, the value of ax_0 in the denominator of (37) can be safely ignored and the whole process thereby much simplified

$$h \simeq \frac{ma^2bp^nx_1}{-\log_e p} \tag{51}$$

$$\simeq rzx_1 \tag{52}$$

while

$$h/r \simeq zx_1 \tag{53}$$

Then

$$x_2 \simeq zx_1(1-e^{-rt}) + x_0e^{-rt} \tag{54}$$

$$\simeq x_1[z(1-e^{-rt}) + e^{-rt}] \tag{55}$$

which is the basis of the statement of the ratio x_2/x_1 for vivax malaria where rt is taken as 0 25 and for falciparum malaria where it is taken as 0 4375

Continuing the same simplification:

$$y_2 \simeq x_1\left[\frac{z-(z-1)(1-e^{-ri})}{ri}\right] \qquad (56)$$

and from (55) and (56) a ratio y_2/x_2 can be calculated to be symbolised as d_2. Then:

$$x_3 \simeq x_2[d_2 z(1-e^{-ri})+e^{-ri}] \qquad (57)$$

and

$$y_3 \simeq x_2\left[d_2 z-\frac{(d_2 z-1)(1-e^{-ri})}{ri}\right] \qquad (58)$$

from which a similar ratio of y_3/x_3, called d_3, can again be calculated between x_3 and y_3, and this process can be repeated in successive incubation intervals. Empirical working of actual values shows that the numerical values of d_1, d_2, d_3, etc., are dependent on z, and converge from an origin of 1·0 on a finite limit slightly exceeding 0·5. Corresponding values of d_3, d_4, d_5, etc., are found to be very close to each othe though not identical.

CRITICAL DEGREES OF TRANSMISSION

It has been shown in (27) that the value of x has a lower limiting value of zero, and it will be noted from (28) that this is reached when z_0 sinks to 1·0 or below. This value of the reproduction rate may therefore be described as the critical rate, in that it separates those values which would result in maintained transmission from those which would lead to extinction of the disease. The basic reproduction rate, given in (21), can therefore be equated with 1·0 as a critical rate. From this there can be derived critical values of each of the factors involved in it, if it is assumed that factor is variable and the others have a constant value. The concept is best known as the critical density of mosquitoes, which is reached when:

$$m = \frac{-r\log_e p}{a^2bp^n} \qquad (59)$$

Such critical levels can only be of interest in relation to control, or conditions of very low endemicity, when the influence of immunity can be ignored and both r and b can be looked on as constant with values of about 0·0125 and 1·0 respectively. An appreciation of p, a and n only is then needed for an understanding of the approximate value of the critical level. It may be converted into a number of other forms. The critical frequency of bites per night, ma, is:

$$\frac{-r\log_e p}{abp^n} \qquad (60)$$

The critical value of the man biting habit, a, is

$$\frac{-r\log_e p}{mbp^n} \tag{61}$$

The critical expectation of life is difficult to state in this form but can be estimated graphically with ease from the fact that it is reached when

$$\frac{p^n}{-\log_e p} = \frac{r}{ma^2b} \tag{62}$$

THEORY OF CONTROL

The theory of control is derived entirely from the critical value of the basic reproduction rate In relation to breeding control or deviation of anophelines to cattle the theory involves nothing more than the application of expressions (59), (60) or (61) In relation to imagicidal control it becomes complicated by the fact that such control modifies both mosquito density, m, and expectation of life, p, while the latter appears in the reproduction rate in two forms as p^n and as $-\log_e p$ The subject can be approached in the following way

Let the daily output of mosquitoes, in relation to the density of people, be termed K Then

$$m = \frac{K}{-\log_e p} \tag{63}$$

and

$$K = m(-\log_e p) \tag{64}$$

Expression (63) may be inserted in that for the basic reproduction rate given in (21) to read

$$z_0 = \frac{Ka^2bp^n}{r(-\log_e p)^2} \tag{65}$$

If control is to be achieved this must be equated with 1 0 by substitution of a second value, p_2 for the original ruling value of p, which may be termed p_1 In that case the value of p_2 must be such that

$$\frac{p_2^n}{(-\log_e p_2)^2} = \frac{r}{Ka^2b} \tag{66}$$

and by substitution of (64) in this it is required that

$$\frac{p_2^n}{(-\log_e p_2)^2} = \frac{r}{ma^2b(x-\log_e p_1)} \tag{67}$$

Values for the right side of this expression may be estimated, once again taking r and b as constants, from which the required value of the

left may be found, and the corresponding value of p read off from a graph of values The following figures may be helpful in preparing such a graph for cases where $n = 12$, as is commonly the case

p	$\frac{p^{12}}{(-\log_e p)^2}$	p	$\frac{p^{12}}{(-\log_e p)^2}$
0 95	205 4	0 70	0 108
0 90	25 4	0 65	0 0307
0 85	5 38	0 60	0 0084
0 80	1 38	0 55	0 0022
0 75	0 38		

PROBABILITY OF MOSQUITO SURVIVAL

(a) *Ratio of immediate and delayed sporozoite rates* If n is not less than 12, s_1 is the immediate sporozoite rate, and s_2 the sporozoite rate taken amongst mosquitoes kept for 12 days after capture, then

$$s_1 = \frac{p^n ax}{ax - \log_e p} \qquad \text{(see 7)}$$

while it can readily be shown that s_2 is represented by

$$s_2 = \frac{p^{n-12} ax}{ax - \log_e p} \qquad (68)$$

because it represents all that proportion which were infected with parasites, including those which had not then developed to the stage of sporozoites, at the time of capture The ratio of these two is

$$\frac{s_1}{s_2} = p^{12} \qquad (69)$$

on the basis of which Figure 11 is drawn

(b) *Ratio of sporozoite rate to the total infection rate* If the period of development of sporozoites is n days, and that of oocysts to the stage at which they can be detected is m days, then by application of the expression (7) for the sporozoite rate to each, the ratio between them is equal to $\frac{p^n}{p^m}$ or p^{n-m}. Figure 10 is drawn for the case, thought common, where the values of n and m are 12 and 3 Prolongation of the first is accompanied by prolongation of the other, with the result that the value of the ratio does not greatly alter with changes in the time of the extrinsic cycle

The general subject of mathematical epidemiology is well reviewed in —

BAILEY, N T J Some problems in the statistical analysis of epidemic data 1955 *J roy statist Soc*, 17, 35–58

SERFLING, R E Historical review of epidemic theory 1952, *Hum Biol*, 24 145–166

The present theory is based on material elaborated in the following papers —

MACDONALD, G The analysis of infection rates in diseases in which superinfection occurs 1950 a *Trop. Dis Bull*, 47, 907–915

MACDONALD, G The analysis of malaria parasite rates in infants 1950 b, *Trop Dis Bull*, 47, 915–938

MACDONALD, G The analysis of the sporozoite rate 1952, *Trop Dis Bull*, 49 569–586

MACDONALD, G The analysis of equilibrium in malaria 1952, *Trop Dis Bull*, 49 813–829

MACDONALD, G The analysis of malaria epidemics 1953, *Trop Dis Bull*, 50, 871–889

MACDONALD, G The measurement of malaria transmission 1955, *Proc roy Soc Med*, 48, 295–301

ARMITAGE, P A note on the epidemiology of malaria 1953, *Trop Dis Bull*, 50, 890–892

APPENDIX II

TECHNIQUES

A KNOWLEDGE of the normal techniques of entomology and parasitology is presumed. The techniques described here include methods of staining films and recording splenic enlargement which are suitable for field work, and those other techniques mentioned in the text which cannot be classified as normal and readily available to the malariologist.

STAINS FOR BLOOD FILMS

Choice of stain largely depends on the individual, Field's, Jaswant Singh's and Giemsa may all be appropriately used in survey work. Field's stain consists of two solutions:

Field's A:

Methylene Blue	0·8 g.
Azure I	0·5 g
Disodium Hydrogen Phosphate (anhydrous)	5·0 g
Potassium Dihydrogen Phosphate (anyhdrous)	6·25 g
Distilled Water	500 ml

Field's B:

Eosin	1·0 g
Disodium Hydrogen Phosphate (anhydrous)	5·0 g
Potassium Dihydrogen Phosphate (anhydrous)	6·25 g
Distilled Water	500 ml.

The salts are first dissolved, the stain is added and solution of Azure I aided by grinding in a mortar. The stain is set aside for 24 hours, filtered, and then used. The prepared film is dipped into solution A for 1 second, gently rinsed in clean water for a few seconds till stain ceases to flow from the film, dipped for 1 second into solution B, gently rinsed for 2 to 3 seconds and placed vertically in a rack to dry.

Jaswant Singh's stain consists of two comparable solutions:

Solution A:

Medicinal Methylene Blue	0·1 g
Potassium Dichromate	0·1 g
Sulphuric Acid, 1% solution, v/w	0·6 ml
Potassium Hydroxide, 1% solution, w/v	2·0 ml
Water	100 ml

The methylene blue is dissolved with shaking, and first the acid and then the chrome salt are added The product is shaken and kept on a boiling water-bath for some hours, till about 1 hour after the colour has turned blue It is cooled, alkali is added drop by drop and whilst shaking to dissolve the needle like precipitate The solution is filtered repeatedly through the same paper

Solution B

Eosin water soluble	1 0 g
Distilled Water	500 ml

A bowl of rinsing water is also needed, the pH having been adjusted to lie between 6 0 and 6 6 by the addition of buffer salts The thick film is immersed in solution A for 10 seconds, washed in the acidulated water for 2 seconds, stained in solution B for 1 second, washed in the same rinsing water for 5 seconds, immersed again in solution A for 10 seconds, again washed for 2 seconds, dried and examined

These two stains can be either compounded or bought ready prepared, and can be used continuously to stain large numbers of slides Giemsa stain cannot be compounded in the ordinary laboratory and must be used fresh each time Staining is best carried out on racks rather than in staining dishes The exact dilutions giving the best results need checking with each batch of stock stain, but usually a 6 per cent dilution is appropriate The dilution is made in distilled water which has been buffered to pH 7 2 The requisite quantity is pipetted on to the film, after 3 to 5 minutes it is agitated to remove dissolved haemoglobin from the neighbourhood of the smear, after 40 minutes stain is gently washed off, the smear is immersed in water for 10 to 15 seconds and then allowed to dry

Many techniques have been used for counting parasites, but the best is probably by observation of the ratio between parasites and leucocytes, associated with a leucocyte count where accuracy is needed Rough estimates only are possible without individual counts of leucocytes, and it is not to be assumed that the mean density in temperate countries prevails in the tropics In one series examined for this purpose in Nigeria the mean was found to be 12,000 per mm^3, *the standard* deviation 5,000, and the range 6,500 to 45,000

THE SPLEEN RATE

Unless qualified by explanation the term spleen rate is understood to mean the percentage of children aged from 2 to 10, inclusive, in whom the spleen is palpable when the child is examined in the standing position Children are mustered by methods appropriate to the locality,

and identification details recorded. The child is examined standing, clothing round the abdomen having been loosened or removed. The examiner's left hand is placed behind the child, below the left lower ribs and gently pressed forward; the right hand is placed flat on the abdomen and an effort made to palpate the lower edge of the spleen with the side of the index finger; if it is not felt, special examination is made for a small spleen with the child breathing deeply, and also for an unusually large one the edge of which is below the part normally palpated. The most valuable information is derived from a simple record of the percentage showing enlargement, but many workers prefer to elaborate this with a statement of the degree of enlargement, in the individual and as an average. The most suitable mechanism is that devised by Hackett; the vertical descent of the apex is recorded in relation to an imaginary line descending from the point where it normally passes the costal margin, and on the following code:—

Class 0: Normal or impalpable spleens.
1: Spleens not reaching the costal margin, but palpable.
2: Spleens passing the costal margin but not projecting below a horizontal line halfway between it and the umbilicus.
3: Those passing this line but not going below the umbilicus.
4: Those going below the umbilicus, but not below a horizontal line halfway between it and the symphysis pubis.
5: Spleens projecting lower than those in Class 4.

The average enlarged spleen is the total of the number of children in each group multiplied by the weight of the group and divided by the number of children examined.

ANOPHELINE CAPTURES

Captures may be made by day or night, in houses or animal shelters, or outdoors, as may be appropriate to the object. When live capture is needed it is best done by means of some form of sucking tube, typically a glass tube $6 \times 1\frac{1}{4}$ in. closed at each end with a rubber bung through which passes a glass tube $\frac{3}{8}$ in. in diameter, 6 in. long at one end and 2 in. at the other; a length of rubber tube and mouthpiece are connected to the shorter, which is closed with a cotton-wool plug. Mosquitoes are picked off the wall by sucking them into the central tube and are later transferred to test tubes closed with cotton-wool plugs. Mosquitoes are transferred as soon as possible to cages made of 5 or 6 square wire frames tied together to form a cube, with a fitted netting cover in which there is a sleeve for admission and removal of insects

Cages are protected from heat, sunlight, wind and dryness, and of course preferably in a room selected and maintained for the purpose, in which an equable temperature and a consistent high humidity of about 80 per cent is kept up If this is not possible they may be kept in boxes, a large piece of dampened cotton-wool being placed on top of the cage

Where mosquitoes are not required alive, and especially where a count of their numbers is wanted, they are best collected with the help of an immediate insecticide There are several detailed methods, a white sheet may be placed on the floor of the closed room which is then sprayed throughout, the sheet being examined and any mosquitoes on it removed after a few minutes A small sheet 18×18 in may be threaded on to two handles which hold it as a square and project about 1 ft at one side This can be carried immediately along the wall and underneath a hand spray from which insecticide is distributed Either of these two methods is likely to give larger catches than the systematic search of a room and removal of mosquitoes discovered with a sucking tube or test tube, but the specimens are more difficult to identify, and are dead

MOSQUITO SURVIVAL RATES

No direct means of measuring the age of individual mosquitoes is known A means has been proposed, and is based on measurement of the degree of fraying of the wing fringe, but the degree of error is so great as to invalidate it for most purposes Indirect approaches in which the age composition of whole populations is determined hold more prospect of success and take the form of estimation of the proportion of the population falling within a known age group If it is assumed that there is no great variation of mortality with age, which often seems justifiable, an estimate of the survival rate can be made from such an analysis Two techniques have been used successfully, but the subject is new and there is ample room for the development of fresh approaches

The ratio between the immediate and the delayed sporozoite rates gives a very valuable measure, but is only usable where the sporozoite rate is moderately high and mosquitoes are numerous A considerable number are captured and divided at once into two groups One is dissected immediately and a sporozoite rate is determined, the other is held for 12 days, or other period not exceeding the extrinsic cycle, and survivors are then dissected and a second, delayed, sporozoite rate calculated The second rate exceeds the first by the proportion of mosquitoes which were incubating parasites at the time of capture but had not then developed sporozoites The ratio of the immediate to the delayed rate is directly related to the mosquito survival rate in a simple

logarithmic form If the probability of survival through one day is called p, and the period for which the second batch was held n, then

$$\log p = \frac{\log \text{ratio}}{n}$$

an equation which can readily be solved to give the value of p with the help of ordinary logarithm tables

A similar relationship holds between the value of p and the ratio between the oöcyst rate and the total infection rate, taken immediately after capture, with the difference that

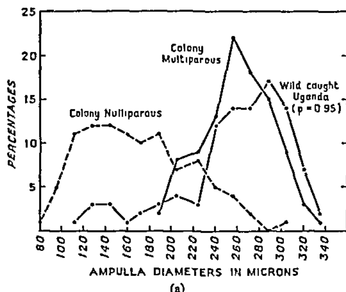
$$\log p = \frac{\log \text{ratio}}{n-3}$$

where n is the time of the extrinsic cycle, the reason for the change being that oocysts are rarely identified before they are 3 days old These two ratios are illustrated graphically in Figures 10 and 11

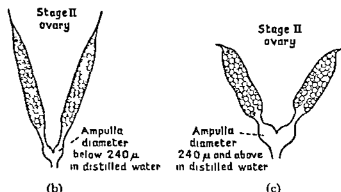
Davidson, examining colony-bred *A gambiae*, noted variations in the size of the ampulla of the oviduct which can be used in a comparable manner, and his method does not turn on the finding of large numbers of infected mosquitoes and so is more generally applicable The median diameter of the ampulla, dissected in osmic acid, was 160 microns in nulliparous mosquitoes with ovaries in Stage III, the commonest and most readily recognised stage encountered in nature In this stage the egg contains yolk granules sufficient to obscure the nucleus, the egg is, however, still ovoid and not elongated as in the mature egg In parous mosquitoes the median diameter was uniformly higher, and to such an extent that no more than a negligible proportion of parous mosquitoes in ovary Stage III had ampulla measurements less than the median in nulliparous In a natural community the proportion of Stage III *A gambiae* in which the ampulla measures less than the median value for nulliparous represents half of the nulliparous proportion This latter can be easily calculated, and from it the parous proportion

To make the measurement mosquitoes are lightly anaesthetised and put on a slide with a drop of 1 per cent osmic acid solution The abdomen is broken by gentle traction between segments 7 and 8, the eighth segment—which can be distinguished by the presence of the spermatheca—is gripped with a pair of very fine forceps, the thorax is held with a broad bladed needle, and the two separated, the hind gut and common oviduct coming with the terminal part Davidson describes the subsequent technique as follows

"With an unfed or newly fed mosquito with ovarian development not later than stage II (Christophers, 1911), it is often possible by



(a)



(b) (c)

Fig 16 The ampulla and its relation to anopheline parity

(a) Frequency distribution of ampulla diameters in colony nulliparous and multiparous *A gambiae* with measurements from a wild caught population superimposed
(b) Reproductive system of a nulliparous *A gambiae* (up to 5 days old)
(c) Reproductive system of a multiparous *A gambiae* (over 5 days old)

further gentle traction to draw out the whole of the alimentary and reproductive systems This is usually possible with a mosquito which has taken only one feed, and is invariably possible with one which has laid eggs With very young mosquitoes with ovaries in stage I, however, the adherence of the tracheae to the surface of the ovaries causes a breakage of the reproductive system somewhere posterior to the ovaries, which are left in the main part of the abdomen In this case—and with a little practice one is able to predict that such adhesion

is present before breakage occurs—it is necessary, after the preliminary break between segments 7 and 8 has been achieved, to sever the pleurae of segments 6 and 7 with a fine-bladed needle and to tease out the ovaries, cutting away the tracheae. This adhesion in itself indicates that the mosquito is newly emerged and therefore nulliparous

"Reproductive systems with ovaries in stage III can usually be extracted in their entirety by a combination of pulling at segment 8 and easing the ovary through the break in segment 7 by gently pressing the sides of the main part of the abdomen

"The extraction of ovaries in stages IV and V is more difficult, as breaking usually occurs with traction, the abdominal aperture of segment 7 being usually too narrow for the passage of the ovaries They can, of course, be removed by cutting the pleurae of the segments anterior to segment 8, but a more rapid method, if the ampulla only is required, is to pull the eighth segment away from the seventh, and then to sever the lateral oviducts just below the ovaries

"After extraction of the reproductive system as a whole or in part, the common oviduct is cut away from its connection with the body wall at the anterior edge of the eighth segment With ovaries in stage I or II the ampullae usually lie flat and undistorted, and can be measured without further dissection With ovaries in later stages it is usually necessary to cut the ovaries away at their lateral oviducts, leaving only the common oviduct, the two ampullae and parts of the two lateral oviducts The ampullae will then lie flat and can readily be measured If the whole reproductive system in these later stages of ovarian development is left intact, there is a tendency for the ovaries to shrink back on the ampullae, thus covering them and preventing measurement" (Davidson, G 1955, *Ann trop Med Parasit*, 49, 24–36)

Measurement of the ampulla is made under a $\frac{2}{3}$-in objective with a ×6 eyepiece with an eyepiece micrometer, the average of two ampulla diameters, at right angles to the main axis, being taken

In this series of *A gambiae* it was found that the median diameter in nulliparous Stage II mosquitoes was 160 microns, extremely few parous mosquitoes having ampullae of a smaller diameter In this mosquito, and at warm temperatures, the first Stage III ovary is reached on the fourth day and the gonotrophic cycle lasts 2 days The proportion of those in Stage III which are nulliparous is therefore

$$\frac{p^4}{p^4+p^6+p^8+p^{10} \quad p^\infty} = 1-p^2$$

from which the proportion parous is equal to p^2 and p is the square root of the proportion parous

Controls for the test should include original, intermediate and final tubes containing saline and antiserum, and a parallel series of tubes containing blood extract and saline

A practised operator working in this way, using a glass sheet previously ruled and numbered in grease pencil, and with a 'Plasticine' strip across them to hold the tubes, will put up over a hundred tests in the morning and will have no need for more elaborate apparatus unless really large numbers are to be continuously handled When the more elaborate and precise form of identification is required, special arrangements should be made with a bacteriological laboratory to prepare th antiserum according to the techniques described by Weitz The essenc of the test is similar to that here described, but the need for precisio will usually dictate the need for the test to be carried out in a bacteriological laboratory where such tests are common

SUSCEPTIBILITY OF ANOPHELINE ADULTS TO INSECTICIDES

The following technique, slightly modified from that originally described by Busvine and Nash, was adopted as a standard at the 5th Meeting of the WHO Expert Committee on Malaria, and is here reprinted by permission, from its Report

"1 *Impregnation of Filter-papers*

"The insecticide is dissolved in a non-volatile, clear, mineral oil (Shell 'Risella' oil) and diluted to a suitable range of concentrations (For measuring out small quantities of oil solutions, 10 ml, 5-ml, and 1-ml 'Record'-type syringes should be used, the oil is too viscous to measure accurately by pipette or measuring cylinder) The concentrations tested should be at approximately equal logarithmic intervals For *Anopheles gambiae*, the following should be of the right order DDT at 2 0%, 1 0%, and 0 5%, gamma BHC at 0 04%, 0 02%, and 0 01%, dieldrin at 0 4% and 0 2%

To treat a batch of papers, 3–10 ml of any selected solution is taken and diluted with twice its volume of a volatile solvent [Ether, which was originally advised by Busvine and Nash, may be found unsuitable under tropical conditions] Ethylene dichloride or trichlorethylene (Trilene) will be found most convenient One millilitre of this mixture is then applied to each paper in a spiral way so as to wet the paper as evenly as possible

'The filter-papers used are Whatman No 1, 11 cm in diameter They are treated in groups of 4–6, each paper being laid on the points of 4 vertical pins projecting from a board It will be found that most of the volatile solvent evaporates within a minute After this, the papers

may be taken off the pins and hung up, so that a further group can be impregnated. Papers should be hung for at least 3 hours to allow of further drying and spreading of the oil residue They may then be used for 2 or 3 days after treatment

"2 *Making the Exposure Chambers*

"(a) *Non volatile insecticides (DDT, dieldrin)*

"A strip 3 in (8 cm) wide is cut from each filter paper and rolled up to form the lining of a 3 in × 1 in (8 cm × 2 5 cm) specimen tube The strip is cut slightly eccentrically to leave a wider segment on one side, from which a 1-in (2 5 cm) circle is cut and pinned to the base of the cork Thus, with the cork in place, a cylindrical chamber is formed, with all surfaces lined with treated paper except the glass bottom of the specimen tube

"(b) *Volatile insecticides (gamma-BHC, aldrin)*

"The exposure is made in a treated paper cylinder as before, but to avoid concentration of vapour, the ends are closed with netting only For this purpose, paper or metal collars are made, supporting 1-in (2 5 cm) circles of cotton mosquito netting Each paper is rolled round a pair of these collars and fixed with a strip of adhesive tape

"3 *Exposure*

"Mosquitos in any standard conditions may be used, but it seems advisable to test the least susceptible forms, namely, young females a few hours after a blood-meal They may be reared at 27° C (80° F)

"Robust mosquitos like *Aëdes aegypti* may be handled by sucking tube, but this causes mortality among some species such as *Anopheles gambiae* It is best to collect these in groups of 2 or 3 in test-tubes When a sufficient number has been collected, the exposure chambers are laid horizontally on the edge of a table with the cork (or one netting-covered collar) removed The test-tubes containing the mosquitos are opposed to the mouths of the chambers and are gently rotated so that the insects fly out and settle on the treated paper With care, about 6 mosquitos can be introduced, and the cork (or netting-covered collar) replaced without loss

"The mosquitos are exposed for 1 hour at 27° C, in darkness, with the exposure cylinders upright After this, the insects are transferred to clean, wire mesh cages, supplied with pads of damp cotton wool Mortality counts are made after 24 hours at 27° C (80° F)

"While this technique does not expose the mosquitos to the sort of dry films they would experience in the field, it does ensure that the same sort of insecticide contact is duplicated in all tests, and the consistency of the results obtained on different trials has confirmed the

validity of the test method The space in which the mosquitos are confined is small enough so that fairly uniform contact with the treated surfaces is maintained throughout the exposure period This method is intended, of course, to measure only the ability of the mosquitos to survive contact with the toxicant, not their ability to detect or avoid it

"4 *Replicates and Results*

"Tests at critical concentrations (i e those with partial mortality from which dose/kill graphs can be drawn) should be replicated six times if possible Log-concentrations/probit regression lines are drawn using the average mortalities and the median lethal concentrations can be estimated graphically

"5 *Correction of mortality for mortality in controls*

"Where any significant mortality occurs amongst control insects, the mortality amongst test insects should be corrected by Abbott's formula The percentage or proportion actually recorded is multiplied by

$$\frac{x-y}{x}$$

where x is the percentage (or proportion) surviving amongst the controls, and y that surviving amongst the test insects"

THE EXPECTED PROBIT

The purpose of probit analysis is to convert dose/mortality records into a form in which they can be easily manipulated and interpolations within observed records made, and to give proper weight to the numbers of insects in each experiment and the degree of accuracy to be expected in the individual results Complete probit analysis fulfilling these purposes is a matter of elaborate calculation based on the theory of random [illegible] d here and the reader requir-

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they facilitate interpolation and thus estimation of a median lethal concentration, and give a better understanding of the relationship between mortality in different experiments than can be got by other means

If, as is usually the case where no selection has taken place, mortality is distributed around a median lethal dose in a random manner, the results of dose/mortality experiments plotted on ordinary metric graph paper appear as a sigmoid curve If the findings were numerous, consistent, and over a wide range of doses, a sigmoid line could be drawn through the plotted records and interpolations could be made on it The conditions are, however, rarely fulfilled in sufficient degree to make reasonably accurate curve-fitting of this sort possible The figures

can however, be converted into an alternative notation, log dose and probit mortality, and when these are plotted a normal distribution falls as a straight line It is relatively easy to sketch in a straight line representing a number of plotted values, or to notice any great divergence from the expected pattern The most commonly used procedure is estimation of the median lethal dose, or LD_{50}, by drawing a line representing the plotted values and noting where it crosses the 50 per cent mortality line

The simplest procedure is by the use of printed probit paper which is obtainable commercially * Mortality and dose appear as abscissa and ordinate but on the required scales All that is needed is to plot the results on these scales and fill in by eye a straight line which most nearly represents the whole series of findings The expected mortality from doses other than those actually used can then be read off directly In drawing the line it is to be remembered that greater weight should be given to findings in the region of 50 per cent than those extreme from it, and to tests in which large numbers of insects were employed than to those with few

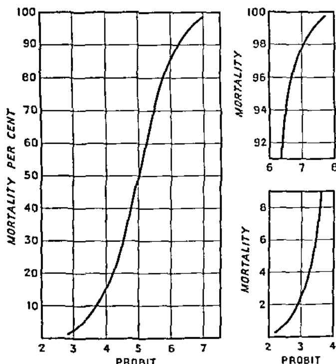


Fig 17 The relationship between percentage mortality and probit value with enlarged sections for mortalities below 9 and above 91

* E g Chartwell Graph Sheet 5573

If printed probit paper is not available the difficulty may be overcome in the following way The doses or concentrations used are first multiplied by 10, 100, or other appropriate figure to ensure that all exceed 1 0 That is, a range from 0 01 to 0 1 per cent is multiplied by 100 to give 1 to 10, to overcome the difficulty of manipulating logarithms of fractions which have a negative value The new values are then represented by their logarithms Mortalities are then converted into their probits, the theory of which is not here attempted Large tables for this conversion are available in the publications mentioned, but a sufficiently accurate conversion for most purposes can be made from the graphs reproduced in Figure 17 The logarithm of the dose is then plotted on metric paper against the probit of the mortality to give an expected probit curve identical with that produced on the more formal printed paper

DETECTION OF RESISTANCE

Discriminating doses, described in Chapter XIV, should preferably be determined by laboratory studies on normal members of the species but pending this the following may be used —(1) 0 4 per cent dieldrin, exposure to which for one hour should kill all mosquitoes except those homozygotes or heterozygotes resistant to dieldrin and γBHC, (2) 4 0 per cent dieldrin, exposure to which for two hours should kill all except homozygotes resistant to dieldrin and γBHC, and (3) 2 5 per cent DDT, exposure to which for one hour should kill all except homozygotes resistant to DDT

The recognition of survivors from exposure to one or more of these treatments, especially (2) or (3), should raise a very strong presumption that resistance is present, and that its prevalence would be exaggerated by selection with the insecticide concerned Until local confirmation of the susceptibility of the normal is available, verification should be sought through examination of the progeny of survivors Every effort should therefore be made to preserve and obtain eggs from them and to rear the eggs to maturity, establishing a colony if possible Resistance to dieldrin and γBHC would be fully confirmed if the first generation of progeny included 25, 50, or 100 per cent of members able to survive exposure to 0 4 per cent dieldrin for one hour, the proportions depending on the nature of the two parents Resistance to DDT would be confirmed if either 50 or 100 per cent of the progeny of a survivor of test (2) could themselves survive the same exposure It might, however, still have been present if none of the progeny could do so, because they might all be heterozygotes which are killed by this dose To guard against error due to this cause it would be necessary to examine the progeny of several survivors of the original test, and if feasible to repeat testing on the next generation

FIELD TESTING OF INSECTICIDES

The essence of field testing, in contrast to laboratory experiment, is that as many as possible of the variables which operate in nature should be left to act, and in particular that the mosquito should not be impeded more than is necessary in its ability to enter and leave the test room or to alight upon and depart from the treated wall surface The wall surface must be constant in each test and it is most important that it should be made of the materials which are commonly used in the construction of houses in the locality Where walls are lined with plaster, whether of mud or other material, particular care should be taken that the plaster is of a type normally utilised and containing the usual proportions of permeable and impermeable matter

The type of test hut which has been found appropriate in Africa is constructed to the local pattern, about 10 ft square, with a thatched or similar roof, *and with a small gap between the roof and the top of the* wall such as normally exists in African houses It has no window, the only formal openings being the door, which must be made to fit closely, and an aperture in the east wall arranged to take a window trap This is a cage, 12–18 in cube, covered with mosquito netting and with a cone-shaped opening on the side inserted in the window, narrowing internally to a diameter of about 2 in The framework is arranged so that it can be fitted readily to the aperture in the window, closing it completely, and so that it can be removed and exchanged for another when collections are made The normal route of entry of mosquitoes is through the small gap under the eaves, and the normal route of departure is in response to an attraction towards light following which mosquitoes fly into the trap through the cone-shaped aperture and are captured in the cage Collections from the trap are made soon after the time at which mosquitoes normally leave houses, usually at dawn Records are preferably made of the numbers of anophelines remaining resting on the wall, dead on the floor of the house, and within the window trap These latter are removed to uncontaminated surroundings and are kept for 12 to 24 hours, when the mortality amongst them is recorded

Ants may cause considerable difficulty in counting anophelines dead on the floor and where this is possible test huts should be erected on a concrete foundation surrounded by a small trench filled with water or disinfectant to prevent the ingress of ants A white sheet spread on the floor the night before catches are to be made greatly facilitates counting those dead in the morning

For any experiment a group of test huts is required One should remain untreated with insecticide and act as a control on the normal mortality to be expected Separate huts would be required for each of

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the insecticides to be tested and for each dosage to be used Insecticide *should be applied with the greatest of care* to ensure evenness of application and accuracy of dosage which should be further checked by placing test papers beforehand on the wall, to be subsequently removed for chemical estimation of the amount of deposit A record should be kept of the dosage intended to be applied and of that actually recorded in the chemical estimation Entry of mosquitoes may be encouraged by ensuring that there is an occupant at night Collections of mosquitoes are made from the wall, floor, and window traps Living mosquitoes whether from the wall or the trap are maintained under ideal and uncontaminated conditions for 12 to 24 hours after capture Results are recorded as the percentage of total mosquitoes captured which are dead either at the time of capture or after this interval of time Comparable counts are made in the check hut to which no insecticide has been applied.

Where any appreciable mortality is recorded amongst the insects collected in the untreated hut the record of kill should be corrected by Abbott's method

CHEMICAL EXAMINATION OF INSECTICIDES

The proper chemical examination of an insecticide requires the knowledge and skill of a chemist and the resources of a fully equipped chemical laboratory It is beyond the scope of a malariologist and should be referred to a chemical laboratory There are, however, a few techniques which should be within his capacity, which demand apparatus of a relatively simple kind, and ability to perform which may considerably enlarge the malariologist's ability to understand some of the materials with which he is dealing, and to inquire into failures or odd happenings in their use The chemist will refer to the WHO publication, *Specifications for Pesticides, Insecticides, Rodenticides, Molluscicides and Spraying and Dusting Apparatus*, in which approved techniques are fully described The tests described below (except the colour test for DDT) are derived by permission from that manual and should be of use to the biologist with an understanding of chemical assay procedures

1 "*Sieving test after tropical storage* Place in a 250-ml beaker of 6–6 5 cm (2 4–2 6 in) internal diameter, 20 g of the concentrate and level off without compacting Place within the beaker, on the top of the concentrate, a loose-fitting piston or disc so formed and weighted as to exert upon the concentrate an even pressure of 25 g per cm^2 (0 356 lb per sq in) Keep the powder thus under pressure *in an oven* at 55° C (131° F) with a minus tolerance only of 2° C (3 6° F) for 24 hours Take the sample from the oven, remove the pressure assembly, and allow the powder to come naturally to room temperature in a closed container

'Prepare a 74-micron sieve (BS sieve No 200, US Standard No 200) by freeing it from any film, grease, or other water repellent material Mix to a slurry with 100 ml and wash the residue with an oscillating, moderately vigorous spray of water (using a rubber hose of 10 mm internal diameter and a stream of 4–5 litres of water per minute) for 10 minutes or until the solid has passed through the sieve Transfer the residue to a Gooch crucible, dry, and weigh Calculate the percentage residue on the screen"

2 "*Suspensibility after tropical storage* Subject 20 g of the material to tropical storage as above Exactly 3 hours after removal from tropical storage weigh accurately into a 250 ml beaker an amount to form 250 ml of a 2 5% suspension of DDT Paste with 30 ml of standard hard water* at 30° C ± 1° C (86° F ± 1 8° F) and allow to stand for 15 minutes at the same temperature Rinse the slurry with standard hard water of 30° C ± 1° C (86° F ± 1 8° F) into a 250-ml graduated cylinder (18 3 1 1), fill up to the 250 ml mark, and close with the stopper Invert the cylinder sharply through 30 complete cycles within one minute During agitation the cylinder must be thermally insulated from the hands to maintain the prescribed temperature in the suspension. Allow the graduated cylinder to stand for 30 minutes in a water-bath at 30° C ± 1° C (86° F ± 1 8° F) Care must be taken that the bench on which the experiments are carried out is protected against vibration *At the end of the settling period (30 minutes) insert the* glass tube (18 3 1 2) into the cylinder and with the minimum of disturbance, withdraw during 10–15 seconds by means of the vacuum pump nine tenths of the suspension, i e 225 ml This is achieved by maintaining the tip of the glass tube just below the sinking top level of the suspension

'Note Should excessive flocculation occur during the test, accompanied by the appearance of transparent liquid, the material is unsatisfactory

"Determine the amount of DDT in the remaining one tenth of the suspension including the sediment by one of the conventional methods

$$\text{Per cent suspensibility} = \frac{(b-a) \times 10 \times 100}{b \times 9}$$

where a = weight of DDT found in the remaining one tenth of the suspension,

b = weight of DDT in the sample used for the test"

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* Calcium chloride anhydrous	0 304 g
Magnesium chloride hexahydrate	0 139 g
Distilled water to make	1 litre

3. "*Estimation of hydrolysable chlorine in technical DDT.* Weigh accurately approximately 0·5 g of the sample of DDT into a 250-ml Erlenmeyer flask. Add 50 ml of acetone and 20 ml of 1 N ethanolic potassium hydroxide. Keep at 20–25° C (68–77° F) for 15 minutes. and add 50 ml of distilled water. Add 20 ml of 2 N nitric acid, exactl 25 ml of 0·1 N silver nitrate, and coagulate the precipitated silve chloride by digesting on a steam bath for half an hour with frequent stirring. Cool and filter the coagulated silver chloride through a fast paper and wash thoroughly with distilled water. Add 5 ml of 10 per cent. ferric-alum solution and titrate the excess silver nitrate with 0·1 N potassium thiocyanate.

"Alternatively, the end point may be determined electrometrically.

"Subtract the quantity of silver nitrate found in the filtrate from that originally added. The difference will be that required to combine in the sample and subtract it from the hydrolysable chlorine.

$$\text{Per cent. hydrolysable chlorine} = \frac{a \times 0{\cdot}3546 \times f}{w} - b$$

here a = ml 0·1 N silver nitrate equivalent to chlorine found after hydrolysis,

b = per cent. inorganic chlorine in the sample,

w = weight of sample,

f = correction factor $= \frac{T}{A}$

where T = theoretical, calculated value, i.e. 10·0 per cent., for hydr lysable chlorine in pure DDT,

A = apparent value of hydrolysable chlorine in pure, recrystallized DDT determined by the above-described method and using the same reagents."

4. "*Estimation of hydrolysable chlorine in technical BHC.* Weigh accurately approximately 0·3 g of the sample into a 250-ml Erlenmeyer flask. Add 50 ml of 0·5 N ethanolic potassium hydroxide and gently reflux for half an hour. Wash down the condenser with distilled water and allow to cool. Add 20 ml of 2 N nitric acid, exactly 40 ml of 0·1 N silver nitrate and coagulate the precipitated silver chloride by digesting on a steam-bath for half an hour, with frequent stirring. Cool, and filter the coagulated silver chloride through a fast paper and wash thoroughly with water. Add 5 ml of 10 per cent. ferric-alum solution and back titrate with 0·1 N potassium thiocyanate. The end point is the appearance of the red ferric-thiocyanate colour.

"Alternatively, the end point may be determined electrometrically.

and allow to cool Add 20 ml of 2 N nitric acid, exactly 25 ml of 0 1 N silver nitrate, and coagulate the precipitated silver chloride by digesting on a steam-bath for half an hour with frequent stirring Cool and filter the coagulated silver chloride through a fast paper and wash thoroughly with water Add 5 ml of 10 per cent ferric alum solution and titrate the excess silver nitrate with 0 1 N potassium thiocyanate

"Alternatively, the end-point may be determined electrometrically

"Subtract the quantity of silver nitrate found in the filtrate from that originally added The difference will be that required to combine with the hydrolysable chlorine originally present in the BHC Calculate the weight of BHC in the sample by multiplying the weight of chlorine found by 2 73 and from this value calculate the BHC content of the water-dispersible powder

Per cent BHC in the water-dispersible powder

$$= \left[\frac{a \times 0\ 3546 \times 5 \times f}{w}\right] \times 2\ 73,$$

where a = ml 0 1 N silver nitrate equivalent to hydrolysable chlorine in the sample,

w = weight of sample,

f = correction factor $= \frac{T}{A}$ "

7 *Colour test for DDT* This quantitative test for small amounts of DDT is based on the formation of a tetranitrate, which gives a blue colour in the presence of alcoholic potassium hydroxide Quantitative measurement requires the comparison of the final colour with a standard, or its measurement in a colorimeter Comparison with paper standards is convenient though inevitably rough A limited number of such paper standards for use with the Allessandrini test have in the past been available on application to the Malaria Section, WHO, Geneva Accurate work demands an electric colorimeter, standards of colour density can then be prepared with solutions of known strengths of DDT, subsequent comparison from which can be very precise The test described is a modification of the Allessandrini and Schechter-Haller tests which has been found accurate and convenient

DDT is extracted from the material to be examined by petroleum ether, by methods which vary with its nature, 'Sellotape' strips are shaken repeatedly in a stoppered flask with 10 to 15 ml lots of petroleum ether, which is transferred to an evaporating dish and evaporated, on an electric hot plate if it is available

A 1 1 mixture of fuming nitric acid (Sp G 1 5) and concentrated sulphuric acid (Sp G 1 84) is prepared by *carefully* pouring the sulphuric into the nitric acid, *not the reverse*

The dried extract is transferred to a stoppered glass tube, 3 to 4 ml of the acid mixture is added, and a similar amount used to rinse the evaporating dish and added to the tube The tube is placed in a water-bath already heated to and kept at boiling point for 20 minutes, removed and cooled The contents are transferred to a 50 ml volumetric flask containing about 10 ml of distilled water, and the tube is rinsed 3 times with 2 to 3 ml of distilled water which is added to the flask, which should then again be cooled to room temperature

15 ml of pure benzene is then added to the tube, and thence to the flask, which is stoppered and shaken, and to which is then added distilled water to bring the surface to about half way up the neck of the flask. This is left until the material has separated into two layers, the upper being a benzene solution of the tetranitrate

About 10 ml of the benzene extract is pipetted off into a stoppered tube and to it there is added about 3 g of anhydrous sodium sulphate after which it is shaken Exactly 5 ml of this is transferred by pipette to another tube to which is added exactly 10 ml of sodium methylate A blue colour develops slowly After a few minutes the intensity is measured on a photo-electric colorimeter, using an appropriate filter (e g Ilford 621), and the quantity of DDT is read off from the calibration curve prepared from known specimens

Staining techniques are described in the following publications —

JASWANT SINGH, RAY, A P & NAIR, C P J S B stain—its preparation in the powder form and the staining technique 1953 *Indian J Malar*, 7, 267–270

FIELD, J W and SHUTE P G *The microscopic diagnosis of human malaria* Studies from the Institute for Medical Research Federation of Malaya, No 24, 1956

This constitutes an admirable atlas of the parasite in thick films

Special entomological techniques are described in —

DAVIDSON, G A new method of estimating the survival rate of anopheline mosquitoes in nature 1953 *Nature (Lond)*, 172 503

DAVIDSON, G Estimation of the survival rate of anopheline mosquitoes in nature 1954, *Nature (Lond)*, 174 792

DAVIDSON, G Measurement of the ampulla of the oviduct as a means of determining the natural daily mortality of *Anopheles gambiae* 1955, *Ann trop Med Parasit*, 49 24–36

GILL[illegible] of age groups within populations of [illegible] 1954, *Ann*

The standard test of anopheline susceptibility to insecticides which is here quoted is derived from —

WORLD HEALTH ORGANIZATION *Fifth Report of the Expert Committee on Malaria* W H O Technical Report Series No 80, 1954

and the methods of estimation of insecticides are derived from —

WORLD HEALTH ORGANIZATION *Specifications for pesticides, insecticides rodenticides, molluscicides and spraying and dusting apparatus* Geneva, 1956

A full account of a variety of methods of chemical testing, useful to the chemist concerned in insecticides, is included in

GUNTHER, F A & BLINN, R C *Analysis of insecticides and acaricides* London Interscience Publishers Ltd, 1955

Two methods of analysis of small quantities of DDT are given in —

ALLESSANDRINI, M E A rapid method for the detection and determination of small quantities of DDT on sprayed surfaces 1950, *Bull Wld Hlth Org*, 2, 629–636

RICHARD, G Application de la methode Allessandrini modifiee par Lanzing a l'évaluation de très faibles quantités de DDT 1953 *Bull Wld Hlth Org*, 9 813–820

Probit tables are available in —

FISHER, R A & YATES, F *Statistical tables for biological agricultural and medical research* Edinburgh & London Oliver & Boyd 5th Edition, 1957

INDEX

Page numbers in roman numerals refer to the Appendixes which follow page 201.
Page numbers in **bold type** are those on which literature is cited.

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